The National Eye Institute

annual report

FY 1976

ANNUAL REPORT
NATIONAL EYE INSTITUTE
July 1, 1975 - June 30, 1976

FOREWORD

A report completed in fiscal year 1976*, which was commissioned by the National Eye Institute, estimates that the total cost of visual deprivation and blindness in the United States exceeds $5 billion annually. To attack the causes of this staggering economic loss and to lessen the personal hardship and suffering of those afflicted by eye disease, the National Eye Institute, in its sixth year, significantly enhanced vision research through its increased support of both extramural and intramural programs. Never before has the Institute supported or engaged in so many projects aimed at relieving these enormous costs. Of the FY 1976 budget of $50 million, the largest in NEI history, extramural and collaborative programs supported over 600 grants, amounting to more than $35 million in funding. During the year, the intramural level of effort was increased to 89 budgeted positions.

One of the most significant events of the year was the announcement in March of findings from the national Diabetic Retinopathy Study. Initial results from this multi-center clinical trial of photocoagulation provide the first conclusive evidence that treatment can significantly reduce the risk of blindness after the retinopathy has reached a moderately severe stage. A paper presenting these findings was published in the April 1976 issue of the American Journal of Ophthalmology.

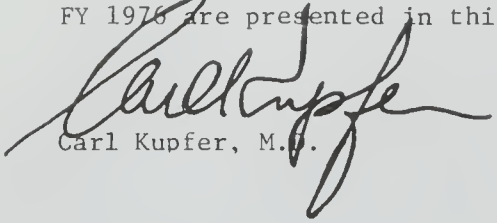
Because of the great importance of the DRS results, the NEI took extraordinary measures to assure their rapid and accurate dissemination to both physicians and the general public once DRS patients had been informed. An advance copy of the AJO paper was sent by the NEI to more than 10,000 practicing ophthalmologists in the United States and the nearly 3,000 physicians who are members of the American Diabetes Association. The DRS is continuing in order to assess the long-term effects of photocoagulation. As further results are obtained, they also will be quickly disseminated to the medical community and to the public.

The NEI followed its program planning initiative with the publication of Support for Vision Research, the Interim Report of the National Advisory Eye Council. This 250-page volume, which presents 80 exhibits documenting available data on research in vision and ophthalmology in the United States for fiscal year 1975, is presently being utilized by the Council's Program Planning Subcommittee and its Program Panels. The Subcommittee will update its earlier

*Westat, Inc., Summary and Critique of Available Data on Prevalence and Economic and Social Costs of Visual Disorders and Disabilities, Unpublished, Rockville, Maryland, February 16, 1976.

delineation of current needs and opportunities in vision research in the Council's second major planning document due for publication next spring.

Research projects, contracts, collaborative trials, and studies initiated, supported, or conducted by the NEI will lead to the diminuation of the physical and psychic suffering of those afflicted with visual disorders and the saving of associated costs. Highlights of the progress made towards this end in FY 1976 are presented in this report.



Carl Kupfer, M.D.

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EXTRAMURAL AND COLLABORATIVE PROGRAMS

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REPORT OF THE ASSOCIATE DIRECTOR FOR EXTRAMURAL AND COLLABORATIVE PROGRAMS
William F. Raub, Ph.D.

Fiscal Year 1976 will be remembered as a "good year" for the vision research community in terms of the fiscal resources available via the National Eye Institute (NEI), but few will forget quickly the many months of uncertainty that preceded the eventual happy outcome. When the year began, the NEI was faced with the prospect of a cutback in funds of approximately 14%--a reduction which at best would have materially slowed progress toward the cure and prevention of vision disorders and at worst would have left many ongoing projects irreversibly crippled. By the last quarter of the year, the prospect of a 14% budget reduction was replaced by the fact of an 11% budget increase; and FY 1976 ultimately became the second consecutive year in which the NEI was able to expand all of its programs so that the community could take advantage of many new research opportunities while simultaneously sustaining the momentum established in other important areas in prior years. The data and observations which follow highlight the status of NEI's extramural and collaborative programs at this new highpoint in the history of vision research.

1. Research Grants[1]

The amount available for NEI research grants during fiscal year 1976 was $35,404,000, an increase of $5,425,000 over the preceding year. This funding level made it possible for the NEI to award 614 grants distributed as follows. This compares with 353 grants in 1970, the first year in which the NEI had its own operating budget.

	Number	Total Awarded (in thousands)
Prior Year Commitments	451	$26,333
Competing Renewals	69	4,624
New Awards	94	4,447

The combined number of competing renewal and new awards represents almost 55 percent of all applications recommended for approval by the National Advisory Eye Council.

[1] As the writing of this report occurred prior to the completion of final FY 1976 funding decisions, the data in this section and the following ones of necessity reflect projected figures as well as actual obligations.

The funding data for NEI research grants is given in more detail below in two complementary ways: by scientific program area, and by funding mechanism.

NEI Research Grants by Program Area

	Number	Total Awarded (in thousands)
Retinal and Choroidal Diseases	239	$12,809
Corneal Diseases	87	6,012
Cataract	70	3,835
Glaucoma	67	5,434
Sensory and Motor Disorders of Vision	151	7,314

NEI Research Grants by Funding Mechanism

	Number	Total Awarded (in thousands)
Project Grants (R01)	535	$31,346
Special Visual Sciences Research Awards (R23)	21	107
Core Center Grants (P30)	11	1,633
Specialized Clinical Research Center Grants (P50)	7	1,321
Research Career Development Awards (K04)	29	684
Academic Investigator Awards (K07)	11	313

The codes given in parentheses in the second table are the NIH-wide symbols used to differentiate the various types of grant awards.

While the foregoing data should be generally self-explanatory, several specific comments on the mechanism table seem appropriate. First, it should be noted that, in keeping with the policy recommendations of the National Advisory Eye Council, the individual research project (R01) remains by far the principal instrument of NEI support; while center grants and other types of awards surely will continue to emerge as important mechanisms for the support of vision research, the NEI is maintaining its traditional emphasis on investigator-initiated, investigator-directed projects. Second, new investigators should be aware that the Special Visual Sciences Research Award (R23) is a mechanism designed especially for them; these "small grants" have helped a number of investigators conduct pilot studies and ultimately build the base of justification for a full-fledged project grant. Third, the Academic Investigator Award, a funding mechanism inaugurated last year, shows good promise that it will achieve its purpose of helping young scientists in academic settings mature as independent investigators; it seems especially well suited to helping clinical investigators establish strong research credentials, and NEI staff intend to exert every effort to insure that this potentiality becomes fact.

2. Research Training

During the past year, the National Research Service Award Program entered its second year. This funding mechanism provides for both institutional and individual fellowship awards and is intended to replace all of NIH's formal means for the support of research training. For the first three quarters of the year, the NEI and other NIH components were unable to make any new awards under this program because of delays in the legislative reauthorization process. However, once the appropriate authorizations were received, it proved possible to add 9 new institutional and 46 new individual awards to the portfolio of active research training activities. The present status of NEI's research training activities is given in the table below:

	Number	Total Awarded (in thousands)
Postdoctoral and Special Fellowships	1	11
Weinberger Fellowships	8	114
Graduate Research Training Grants	25	1,686
National Research Service Awards (Individual)	57	649
National Research Service Awards (Institutional)	31	2,187
Totals	122	4,647

The array of research training efforts tabulated above provides an effective complement to NEI's other forms of research support. The principal goal of these research training awards is to equip young men and women with the range of skills, experiences, and insights necessary for them to compete successfully subsequent to their training period for research support from NIH and other sources, and thereby embark on careers as independent scientists. Moreover, the research training program is viewed as a nearly ideal vehicle for strengthening the ties between the clinical aspects of vision research and other disciplines such as those of basic medical sciences, epidemiology, and biomathematics.

3. Collaborative Research Activities

The NEI's collaborative research activities, funded through the contract mechanism, continued to place emphasis on cooperative clinical trials of therapies for diabetic retinopathy. The distribution of contract awards and funds is as follows:

	Number	Total Awarded (in thousands)
Diabetic Retinopathy Study	17	$1,680
Diabetic Retinopathy Vitrectomy Study	6	350
Other	4	292
Totals	27	$2,322

As noted elsewhere in this report in more detail, the Diabetic Retinopathy Study achieved important results during the past year. The study revealed,

based on two-year follow-up data, that photocoagulation therapy is substantially more effective than no treatment in reducing the rate of occurrence of blindness in three subgroups of eyes: (a) those with moderate to severe new blood vessels on or near the optic disc; (b) those with mild new blood vessels on or near the optic disc and evidence of recent vitreous hemorrhage; and (c) those with severe new blood vessels away from the region of the optic disc and evidence of recent vitreous hemorrhage. These results provide a valuable scientific basis for dealing with one of the leading causes of new blindness. The study continues in order to determine the longer term effects of treatment, to compare the two different modalities of photocoagulation therapy used--the xenon arc and the argon laser, and to gain increased understanding of the natural history of diabetic retinopathy.

The Diabetic Retinopathy Study is an excellent example of rigorous scientific investigation conducted in the milieu of health care. Such studies do much to bring about effective translation of research results into clinical practice. The vision research community can be proud of its leadership role in the planning and conduct of cooperative clinical trials.

During the past year, a second cooperative clinical trial, the Diabetic Retinopathy Vitrectomy Study, completed the bulk of its detailed planning phase. This study is designed to determine whether surgical removal of the vitreous body is better when performed within a few months following a massive, non-clearing vitreous hemorrhage rather than the present clinical practice of waiting approximately one year. The study also includes a natural history investigation of the progression of retinopathy in eyes which have useful vision but a bad prognosis due to the presence of extensive fibrovascular proliferations. As of this writing, negotiations are underway to add up to 6 additional clinics to the original complement of 7 clinics, a reading center, and a coordinating center. Recruitment of patients is scheduled to begin during the summer of 1976.

Like the Diabetic Retinopathy Study, the Diabetic Retinopathy Vitrectomy Study has its conceptual and methodologic roots in basic and applied research previously supported by the NEI and other organizations. This trial should contribute further to the translation of research results to clinical practice and should add additional valuable knowledge about both the natural history of diabetic retinopathy and the appropriate timing for intervention via the vitrectomy procedure. Another important characteristic of the study is that a large scale scientific evaluation of a surgical procedure is being conducted soon after the development of the technique and well before its widespread adoption by the medical community.

4. Management Information System

The NEI's management information system continued to develop during the past year as an invaluable tool for the management and administration of extramural and collaborative programs. The scope of the computer-based records on the scientific and fiscal aspects of NEI awards was enlarged to enhance their utility. The improved capabilities in this area proved especially useful in the preparation of the National Advisory Eye Council's interim program planning report--"Support for Vision Research." This report,

a statistical update and extension of the Council's first program planning report published in 1975, provides the vision research community with a detailed accounting from many perspectives on how NEI fiscal resources are allocated. The compilation, organization, and analysis of the NEI data tabulations for this report were facilitated immeasurably by the presence of a strong management information unit.

5. Staff Changes

During the past year, there were several changes in key positions concerned with NEI extramural and collaborative programs.

a. Mr. James G. Culp, Chief of the Contracts and Grants Branch, left the NEI to become the Executive Officer for the Bureau of Quality Assurance, Health Services Administration, DHEW. Ms. Anna Marie Perrell now is serving as Acting Chief of the Contracts and Grants Branch. Mr. Richard Gruber is coordinating NEI contract acitivites.

b. Dr. Michael F. Halasz joined the NEI as Extramural Program Director for Sensory and Motor Disorders of Vision.

c. Ms. Carolyn McHale joined the NEI and assumed responsibility for direction of the Management Information Unit.

d. Ms. Julia Fairall, Grants Management Specialist, left the NEI to accept a comparable position in the Policies and Procedures Office, Division of Contracts and Grants Management, Office of Administrative Management, Alcohol, Drug Abuse, and Mental Health Administration.

RETINAL AND CHOROIDAL DISEASES

The substantive content of the Program is as varied and complex as are retinal and choroidal disorders. Current thought has resulted in an organizational approach as follows:

CIRCULATORY ABNORMALITIES

(a) Disturbances in Circulation

These include alterations in blood supply due to vascular development, obliteration, occlusion, tortuosity and hemorrhage.

(b) Blood Vessel Formation

These include disorders which may be due to environmental influences or hereditary pattern manifestations, such as retrolental fibroplasia and diabetic retinopathy.

DEVELOPMENTAL AND DEGENERATIVE ABNORMALITIES

These include growth and physiology of pigment epithelium, photoreceptors and neural retina and exclude tumors and proliferative blood vessel disorders.

(a) Pigment Epithelium and Choroid
(b) Visual Pigments, Photoreceptors and Transduction
(c) Information Processing

VITREOUS DEGENERATION

These include retinal detachments due to vitreous fiber formation and shrinkage and vitreous liquification and opacification.

MACULOPATHIES

These include disorders of the fovea centralis which result in defects in central visual acuity and depressed color vision.

TUMORS

These include the detection and study of abnormal growth of all cells of the eye globe and related structures.

UVEITIS

This includes disorders of the iris, the ciliary body and the choroid other than their involvement with glaucoma and infectious diseases of the anterior segment.

It is evident of the variety of structures, diseases and disorders dealt with in this Program that selected topics have been chosen for consideration in this report. The topics include the following:

1. Uveitis and Inflammation, including Experimental Allergic Uveitis;

2. Vascular Proliferative Retinopathies, including Retrolental Fibroplasia;

3. Vitamin E and Membranes

UVEITIS AND INFLAMMATION

The health of the neural and sensory retina demands a well-maintained nutrition and metabolism. Although the retina is a thin structure, less than 0.5 mm thick, its complex metabolic requirements are served by dual but interdependent blood supplies. The outer portion of the retina is maintained by a vascular bed called the choriocapillaris which is formed by an anastomosis of the vessels entering the globe at anterior and posterior locations. The choriocapillaris lies posterior to the photoreceptors and the retinal pigment epithelial cells. Therefore, the sensory retina is served by this portion of the vascular system. The inner areas of the retina are served by the central retinal artery which enters the globe with the optic nerve and disc where further branching occurs. The smaller branches of this vascular system are distributed in the nerve fiber and inner nuclear layers. Therefore, the neural retinal is served by this portion of the vascular system.

It is evident that for the normal function of the retina, both blood supply systems must be intact. Each system contributes to a different portion of the retina, and therefore, various parts of the uvea may be involved in disease processes. That part of the uvea which may be implicated in retinal diseases is the choroid which contains the highly vascularized choriocapillaris. New techniques for visualizing the choriocapillaris are an important topic for further investigation.

Due to the presence of structures, such as the pigment epithelial cells, Bruch's membrane, as well as the retina, the choriocapillaris does not lend itself to detailed visualization by ordinary ophthalmoscopic examination or fluorescein angiography. Visualization of the retinal circulation by use of fluorescein is a common clinical tool which has achieved a measure of success due to the fact that blood flow is at approximately a right angle to the viewer or camera. The problem is one of resolving the smallest blood vessels. By contrast, blood flow in the choroid is rapid and in the direction toward the viewer or camera. In addition, light emitted from choroidal vessels is scattered by the tissues which lie between the viewer and the choriocapillaris.

In an effort to resolve these problems, Patz[1] and associates at Johns Hopkins University continue to work on the improvement of choroidal fluorescence angiography. They are modifying and evaluating a multispectral fundus camera for taking choroidal angiograms with improved speed and resolution. It appears that these angiographic techniques may provide the most promising means of

documenting changes in the vasculature of pigmented choroidal tumors and in retinal neovascularization.

Patz and Flower[2] have been using indocyanine green dye in their studies; however, in an effort to improve resolution of choroidal vessels and blood flow studies, a search for another dye has been in progress. Hochheimer[3] of the Johns Hopkins University Applied Physics Laboratory is exploring a series of dyes, other than indocyanine green, in search of one which will permit a simultaneous choroidal and retinal angiogram. The dye which will be suitable for this purpose must have a fluorescent wavelength which is different from that of fluorescein. A large number of dyes have been surveyed for physical characteristics, absorption and fluorescence spectra, solubility, stability in solution, toxicity, and binding of dyes to blood proteins; at the present time, approximately 460 dyes have been screened. The work is now focused on approximately 20 dyes to be further evaluated for toxicology, dye chemistry, and angiography. If a dye is found which will give greater definition of choroidal blood flow and better vessel resolution than does indocyanine green, further consideration should be given to the use of such a dye in conjunction with fluorescein and a multispectral camera.

The choriocapillaris is separated from the retinal pigment epithelium by an organized connective-tissue structure referred to as Bruch's membrane or lamina vitrea. When this membrane is viewed by transmission electron microscopy, its complex morphology becomes evident. The membrane consists of the basal lamina of the pigment epithelium, an inner zone of collagen, a layer of elastic tissue, an outer zone of collagen, and a basal lamina of the endothelial cells of the choriocapillaris. In addition to changes in Bruch's membrane with aging, it would seem that because of its heterogeneity and physical location, consideration should be given to this structure as an active or passive barrier in efforts to study the movement of substances to and from the choriocapillaris and through the retinal pigment epithelium. Furthermore, its spectral properties are a factor which must be considered in studies of choroidal blood flow. Olson[4] at the George Washington University is investigating the sequence of deposition of the various connective tissue elements in Bruch's membrane in the vertebrate embryo. A biochemical characterization of the various elements laid down in the course of fibrillogenesis can be obtained by use of specific histochemical staining reactions for elastin and mucopolysaccharides and by use of specific degradative enzymes such as elastase, collagenase, and mucopolysaccharidases. It is anticipated that study of this structure will have a far-reaching impact on retinal disorders, such as macular degeneration, which may have underlying causes at the level of the blood-retinal barrier.

Altered vascular and epithelial cell permeability is an important factor to be considered as an underlying mechanism in retinal disorders of vascular origin. Another approach to the study of the blood-retinal and chorioretinal barriers has been taken by Smith[5] at the Albany Medical College. The permeability barriers can be demonstrated by use of an electron-dense ultrastructural tracer, microperoxidase. By following the movement of this substance between extracellular spaces, information about the ultrastructural location of anatomical and physiological barriers may be obtained. Microperoxidase is a small molecule with a molecular dimension of 20 Å and molecular weight of 1,900. It is soluble

and nontoxic to cells in the minute quantities used in tracer studies. Experiments with monkeys given intravascular injections of this tracer showed that microperoxidase fills the choriocapillaris and can escape from the capillaries and stain Bruch's membrane. Although minute amounts of the tracer can be found in basal invaginations, microperoxidase did not penetrate the tight junctions of the apical end of retinal pigment epithelial cells. The tracer was not found in the subretinal spaces associated with photoreceptor rod outer segments. This study leaves some questions unresolved, such as tracer aggregation and nonspecific binding to Bruch's membrane and to retinal pigment epithelium.

It is also possible to conjugate fluorescein to dextrans of known molecular size and weight. By use of angiographic techniques, one can follow the behavior of these compounds. Bellhorn[6] and associates at the Albert Einstein College of Medicine have studied leakage of abnormal retinal blood vessels. The fluorescein-labelled dextrans have known molecular weights which range from 3,000 to 70,000. Thus, these investigators have demonstrated another useful methodology for the study of vascular permeability changes in the course of experimental retinopathies. These studies encourage the use of tracer molecules of known size and weight for study of anatomical and physiological barriers which might contribute to blood-retinal and choroidal disorders.

The interactions between the apical end of the retinal pigment epithelial cells and the outer segments of the photoreceptors are not thoroughly understood. In addition, the interaction of the basal end of these epithelial cells with Bruch's membrane has not been completely described in regard to structure and function. An ultrastructural study has been reported by Henkind[7] and associates at the Albert Einstein College of Medicine. The cohesiveness of normal rat retinal pigment epithelium to Bruch's membrane appears to be based upon the existence of desmosome-like attachment sites which connect the plasma membranes of the basal infoldings of individual cells. Desmosomes are thought to be the structures which provide the physical attachment of epithelial cells to each other. These investigators hypothesize that the desmosomes described in this study are critical attachment sites which may be involved in some retinopathies.

EXPERIMENTAL ALLERGIC UVEITIS

Although microorganisms have been implicated as one antigen which may initiate uveitis, pathogenic organisms are rarely isolated from humans with uveitis. Therefore, it is assumed that immune mechanisms are an important consideration in the pathogenesis of this disease. Nevertheless, investigators have categorized the disease into primary and secondary uveitis. The role of herpes virus in recurrent uveitis is under study by Oh[8] and associates at the University of California, San Francisco. They have shown that live herpes simplex virus can be isolated as early as the first five hours after an intravitreous injection of the virus in the rabbit eye. This acute phase of the disease is referred to as primary uveitis. In eyes which recover from the primary phase, a secondary phase of uveitis will develop in which no infectious virus can be detected. Inactivated virus can induce a secondary uveitis which

is manifested by cells in the anterior chamber, iritis, lenticular precipitates and vitreous haze at a later stage. Therefore, it appears that secondary uveitis is the result of immunological mechanisms.

Further evidence of immunogenic inflammation mechanisms has been obtained in the laboratory of Silverstein[9] and associates at the Johns Hopkins University. When ovalbumin and bovine gamma-globulin are injected into the vitreous of the rabbit eye, a long-standing immunologic memory of the antigen is produced. A second injection of the antigen after the inflammation has subsided will cause a recurrence of the uveitis and an antibody response. These investigators present evidence that the uveal tissue behaves in a manner similar to a lymph node undergoing a primary and secondary response to an antigen. The specificity and the kinetics of antibody formation and memory within the uveal tract is a subject for further study and may help to explain recurrent uveitis in the human eye.

Another approach to the problem of uveitis is to provide a laboratory model for autoimmune disease. Meyers[10,11] and associates at the University of California at Los Angeles have been investigating the role of photoreceptor cells and retinal pigment epithelium in the induction of autoimmune uveitis. The antigens used are purified guinea pig retinal rod outer segments and retinal pigment epithelium injected in the guinea pig footpads and intradermal sites. The immunized animals develop the "clinical" picture of anterior and posterior uveitis. The inflammatory reaction in the posterior uveal tract is often accompanied by destruction of the photoreceptor cells. A delayed type of skin hypersensitivity response can be demonstrated when immunized animals are skin-tested with the antigens. These investigators have not been able to induce uveitis with extracts of rod outer segments or pigment epithelium. The antigens are probably membrane proteins. The role of cell-mediated immunity and circulating antibody-immune mechanisms in uveitis and retinal damage is still in progress. Attempts will be made to use purified rhodopsin as the antigen to induce clinical signs of uveitis.

Studies in progress at the University of Louisville have implicated three antigens in the pathogenesis of experimental allergic uveitis. Wacker and Kalsow[12] have been investigating antigens identified as a component of Bruch's membrane which affects the choroid. They have also prepared a sediment from retinal homogenate which does not cause uveitis and retinal homogenate extract which will produce uveitis. The immune responses of the three tissue antigens can be differentiated on the basis of immunofluorescent reactivity. When the antiserum system to guinea pig retinal homogenate extract was evaluated in bovine, rabbit, rat, and human retinas, species specificity was not observed. The immunofluorescent reaction was found to extend from the outer plexiform layer to the outer segments of the photoreceptors.

Kalsow[13] at the University of Louisville has extended the investigation by use of precepitin-line formation in immunodiffusion techniques. The patterns show that the guinea pig antiserum against retinal homogenate extract contains a component which is specific for guinea pig retina and two other components which are common to monkey, guinea pig, human, rat, rabbit, and bovine retinas. The

strength of reaction varies with the species tested. However, the human uveitic patient's serum does not react with homogenates or extracts from guinea pig, bovine, or human retinas.

It may prove difficult to compare and correlate studies conducted in various laboratories because antigens and antibodies are prepared under different conditions in each. Nevertheless, investigations appear to be taking approaches which will lead to the understanding of human uveitis.

RETROLENTAL FIBROPLASIA

The development of new blood vessels on the surface of the retina is an indication of serious pathological conditions. These vessels may proliferate into the vitreous, hemorrhage, alter the transparency of the retina as well as the vitreous, or may cause the retina to be lifted from the choroidal structures if the physical properties of the vitreous should change. The history of retinal vascular changes can be followed by fundus ophthalmoscopy and angiography. Among the diseases which characteristically have retinal neovascularization as a major cause of blindness are retrolental fibroplasia (RLF) in the infant and diabetic retinopathy in the adult. Early diagnosis is essential to prevention and treatment of vascular proliferative retinopathies.

Under the guidance of Flynn[14,15] at the Bascom Palmer Eye Institute, University of Miami, an ophthalmologic investigation of the incidence and course of RLF is in progress. Two groups of premature infants have been identified as high risk. One group suffers from chronic respiratory distress and requires continuous oxygen therapy during the first two weeks of life. The other group suffers from spells of apnea and requires intermittent periods of oxygen therapy. Evidently, RLF is still prevalent among premature infants, and although arterial blood oxygen tension (PaO_2) is monitored, it appears that the occurrence and severity of the disorder do not always correlate with these measurements. Values of PaO_2 greater than 100 mm Hg are believed to be hazardous; however, vascular changes have been found in premature infants with respiratory distress even though PaO_2 levels never exceeded the upper limits. Confirmation of the diagnosis was obtained at postmortem examination. Cases of RLF occurring in spite of all precautions have been observed at the Universities of Miami and Washington and the Johns Hopkins University.

Fundus photography and fluorescein angiography of the premature eye are the techniques used to document the vascular changes in RLF. Prior to the third week of life, there is a vitreous haze which interferes with fundus examination. A goal of the study at the University of Miami is to obtain information which will permit the prediction of which lesions may develop into severe scarring and which may resolve themselves with little or no scarring. Since 1969, the University of Miami clinical population has included over 2,600 babies and several hundred are being studied in greater detail. Fifty-five cases of acute RLF have been diagnosed, and the pathogenesis of the RLF lesion is now in progress. These studies will permit the prediction of those cases of RLF in which vascular proliferation will become more serious or regress in the premature infant.

At Johns Hopkins University, Patz[16] and associates have been studying fundamental mechanisms involved in normal and abnormal retinal vascularization. Perfusion of retinal capillaries has been followed by fluorescein angiography and measurements of arterial oxygen tension (PaO_2). The vasoproliferative response has been studies in large numbers of dogs, cats, and rabbits. Minimal oxygen exposure results in vascular obliteration of the most anterior peripheral vascular complexes, while high oxygen concentration will obliterate the entire retinal vasculature after five days at PaO_2 values greater than 250 mm Hg.

Although the rabbit has a different retinal vasculature structure than humans, it does show the obliterative response to high oxygen tension. However, the availability of a model of neovascularization produced by oxygen and retinal schemia is of significance in the study of proliferative retinopathies. The rabbit model is being used in a study which has been designed to demonstrate the stimulation of an angiogenic factor in the vitreous during vasoproliferation.

It has been shown at the Massachusetts General Hospital that some tumors produce an angiogenic factor. Chen, Finkelstein, and Patz[17] at the Johns Hopkins University have injected suspensions of carcinoma cells into the vitreous of rabbit eyes. The tumor cells appeared to stimulate neovascularization at the surface of the retina, and the retinal vessels penetrated into the tumor. Apparently, some angiogenic factor is liberated by tumor cells placed in the vitreous, and the factor is capable of stimulating retinal neovascularization. The model of tumor angiogenesis may be exploited to help explain the mechanisms underlying neovascularization produced in response to oxygen treatment of premature infants or other toxic insults in adults.

There appears to be a correlation between the concentration of soluble protein in the vitreous and vascularization. As measured in dogs and cats, the amount and concentration of protein in the vitreous decreased as vascularization approached completion in the normal eye. However, when the animals were subjected to hyperoxygenation for four days at three to five days of age, vitreous protein concentration was higher than normal and may have been associated with capillary closure and neovascularization. It is hypothesized that hypoxia induces the formation of a vasoproliferative factor. The problem is to isolate and assay the angiogenic factor which may have accumulated in the vitreous. A bioassay technique involves the injection of vitreous into a micropocket of the rabbit cornea at the limbal region and observation of scleral vessels proliferating through the limbus into the cornea. It has been found that vitreous from hyperoxygenated puppies shows extensive vascular proliferation while saline and normal vitreous controls are essentially without effect.

VITAMIN E AND MEMBRANES

Several ongoing studies are testing the hypothesis that vitamin E (alpha-tocopherol) may have a protective action against the toxic effects of oxygen in infants at risk for retinal vasoproliferation. The possible role of vitamin E has been mostly ignored due to the belief that oxygen is the causative agent in RLF. However, it appears that oxygen is not the single causative agent. The premature infant may be suffering from vitamin E deficiency due to poor absorption from the gastrointestinal tract. The theory is that antioxidants, such

as vitamin E, could protect retinal tissues from toxic photochemical events in the presence of high oxygen tensions which may lead to irreversible membrane changes and events of RLF. The premature infant may be deficient in vitamin E, and therefore, the infant may be more susceptible to retinal cell death and neovascularization.

Phelps[18] at UCLA has designed a study to use the newborn kitten as a model for human RLF. The first phase of the study will determine the minimal level of oxygen therapy at which reproducible retinal pathology can be obtained in nearly all exposed kittens. After the minimal toxic oxygen level is determined, the role of vitamin E will be studied in treated and depleted kittens which receive oxygen therapy. Preliminary results have shown that in 37 kittens, experimental RLF is a consistent occurrence after 32 hours of oxygen exposure; the severity increases with time. Intramuscular administered daily doses of 50 mg of vitamin E per day was tested on 32 kittens which were exposed to high levels of oxygen. After 58 hours of hyperoxia, a beneficial effect of vitamin E was demonstrated. After 90 hours of hyperoxia, the difference between the vitamin E treated and placebo controls was no longer evident.

Another approach to the question of the role of vitamin E in the maintenance of membranes is being undertaken by Dratz[19] and associates at the University of California at Santa Cruz. They have hypothesized that light and oxygen-induced membrane degeneration may be due to lipid oxidation. Similarities may be drawn between blood vessel cells and membranes and photoreceptor membranes. These investigators have reported that purified preparations of rod outer segments show an increase in membrane fragility in the presence of oxygen. The addition of vitamin E to preparations reduced the susceptibility to oxygen damage. The products formed by oxygen damage correlate with and appear to be due to oxidative damage to polyunsaturated fatty acids in membranes and possible damaging effects of lipid oxidation products. The value of this work relates to the role of vitamin E and its possible protective action in membranes. Study of the mechanistic role of vitamin E in the prevention of oxygen toxicity may produce information about basic biochemical mechanisms which may apply to all membranes.

Lipid oxidation may be a major degradative reaction in membranes exposed to light and oxygen, as in the disorders of RLF, as well as retinitis pigmentosa. Preliminary experiments have suggested that changes in the fragility and leakiness of membranes may relate to lipid peroxidation. Cell membranes are more susceptible to the effects of lipid peroxidation, and susceptibility to membrane effects may increase if the animal is nutritionally deficient in vitamin E. Furthermore, the toxic products of lipid peroxidation may exert their effects on structures other than at the site of the biochemical reaction. Therefore, lipid peroxidation in conjunction with photodynamic action and oxygen may induce degeneration and tissue damage in blood vessel walls, photoreceptor membranes, retinal pigment epithelium, Bruch's membrane, or choriocapillaris. The removal of oxygen or the addition of antioxidants (vitamin E) may afford some protective action. The elimination of the toxic effects of lipid peroxidation by reliable and safe means, such as ingestion of vitamin E, will help to maintain membrane-dependent visual processes.

Another approach to the role of antioxidants (vitamin E) in the maintenance of membranes involves a study of the effects of dietary deficiency in weanling kittens. Hayes[20] at the Harvard School of Public Health plans to extend his earlier studies of vitamin E conducted in dogs and monkeys. In the earlier studies, vitamin E deficiencies resulted in an accumulation of lipofuscin in the retinal pigment epithelium as well as other extensive pathological changes in vascular endothelial cells.

Accumulation of lipofuscin relates to several retinal disorders which may have their basis in membrane and enzyme disorders, such as macular degeneration, vascular problems and retinitis pigmentosa. In relation to the latter disorder, Hayes and associates have demonstrated that taurine is required by the cat for maintenance of a functional retina; however, little is known about the metabolism or specific role of taurine in membranes. The current approach to the problem will involve a comparison of taurine and vitamin E effects on the maintenance and function of membranes and the accumulation of peroxides (lipofuscins) as related to pathological changes. If it can be clearly demonstrated that vitamin E has a protective effect in animal models, studies involving humans should be considered.

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CORNEAL DISEASES

INTRODUCTION

Diseases of the cornea,associated with appreciable morbidity and pain, produce unilateral impairment of vision in a number of people, and often occur in relatively young patients.

CORNEAL ENDOTHELIUM

The transparency of the cornea is largely maintained by a single layer of endothelial cells which lines its posterior surface. Damage to this cellular layer interferes with its physiological function, with resultant edema and visual loss. Histopathological studies, using fixed, stained flat preparations of the cornea, have shown morphological changes in the cells of the endothelium associated with age, inflammation, and ocular disease. Unfortunately, information correlating these morphological changes with abnormal physiological function in vivo is rather limited.

In the past, diagnostic information about the in vivo endothelium could only be obtained by observing the specular region of reflection from the endothelium with a slit lamp biomicroscope instrument developed by Maurice.

Laing, Sandstrom and Leibowitz at Boston University[1] have developed an instrument and a technique for a direct microscopic visualization and photography of the corneal endothelium in vivo. The technique is applicable in animal experimentation and for diagnostic observation and clinical research in human beings. The endothelial photomicrography requires only a topical anesthetic and modification of the suction contact lens in general clinical use. Since the technique enables noninvasive observation and permits study of the endothelial cells in living individuals, documentation of morphological changes can be made over a period of time. One can assess whether these changes represent the normal aging process, the results of disease or surgical trauma, or a response to specific controlled experimental stimuli.

Stoker reported in 1971 that the regenerative capacity of rabbit corneal endothelium is far greater than that of the human. In rabbits, complete endothelial healing following extensive damage occurs rather rapidly, whereas in humans, endothelium may fail to regenerate completely following injury. VanHorn and Hyndiuk[2] at the Medical College of Wisconsin found that non-human primates may be a better model for studies of endothelial regeneration than the rabbit. They reported that extensively injured non-human primate corneal endothelium regenerates in seven to nine days and the pattern of the repair is similar to that of humans.

CORNEAL STORAGE AND TRANSPLANTATION

A research advance that was directly applied to longer storage of corneas for eye banks, was achieved by Kaufman and McCarey in 1974. The M-K medium (or tissue culture 199) for long term storage and preservation

of donor corneas has been increasingly used and several research teams have reported very promising results using this medium with storage time up to 80 hours.

Detailed basic work on the properties of corneal tissue kept in this medium were reported by Bigar, Kaufman, McCarey and Binder[3] at the University of Florida. By radioactive labelling techniques and autoradiography, these investigators showed the persistence of labelled endothelial cells in the central zone of the grafted corneal button (previously stored in M-K), with the labelled cell density being equivalent to controls with fresh tissue. Clinical studies on the M-K medium conducted at Johns Hopkins University by Stark, Maumenee and Kenyon[4], have also shown that after prolonged storage in M-K medium the endothelium remains intact. The ability to maintain corneal tissue in storage without significant loss of viability does much to reduce the frequency of early graft failures (especially in aphakic eyes).

Aquarella, Van Horn and Haggerty[5], at the Medical College of Wisconsin, evaluated human eye bank corneas preserved in M-K medium by vital staining, histological methods, and scanning and transmission electron microscopy. These investigators reported corneal endothelial viability and ultrastructural integrity after up to four days of storage. In twenty-five consecutive keratoplasties performed with human cornea grafts which had been stored in M-K medium, 92% of the grafts were clear and normal in thickness.

The prolonged storage of corneas which the M-K medium makes possible has several advantages. The prospective keratoplasty recipient can wait at home until suitable donor material is obtained, and surgery can then be scheduled with regular operating room personnel. Also, the added time permits tissue typing and antigenic matching of donor and recipient in selected cases, and it facilitates the transporting of donor material among eye banks.

Despite the advances noted above, corneal graft rejection remains a serious problem. Although graft rejection is primarily a result of cellular immunity, it seems that preformed antibody against a graft decreases the chance for its survival. It is known that in transplants of tissue,other than corneal, acute rejection is often due to ABO (blood group) antibody. Decreased survival of the graft over a long period seems also to be true. Since ABO antigens are represented on most cells, ABO mismatches between donor and host should be harmful to the transplanted cornea either immediately or later.

Allansmith, Drell, Kajiyama and Fine[6], at Stanford University School of Medicine, have discounted the suggestion that compatibility of the ABO blood groups between donor and host is of importance in corneal transplantation. Their study of 150 corneal grafts examined for ABO type revealed that 25% of the grafts were corneas from incompatible donors. Recipients with histocompatible sensitization exposures such as prior corneal transplant, one or more pregnancies, or one or more blood transfusions were no more likely to experience graft failure if the graft were from an ABO incompatible donor than from a compatible donor. No detrimental effect of transplanting across the ABO barrier could be proven by these investigators.

Lamellar keratoplasty seems to offer a good chance of restoring useful visual acuity to patients with recurrent granular dystrophy who have had prior full-thickness grafts. Stuart, Mund, Iwamoto, Troutman, White and DeVoe[7], at Columbia University, have studied full-thickness corneal buttons from four patients with granular corneal dystrophy who previously received transplanted corneas. These investigators presented important suggestions for the treatment of this corneal disease. They found that donor keratocytes appear to remain for many years following grafting in cases of recurrent granular dystrophy and suggest that a superficial lamellar keratoplasty is preferable to a full thickness grafting.

CORNEAL VASCULARIZATION AND WOUND HEALING

Significant data on corneal vascularization had been obtained by Fromer and Klintworth[8] at Duke University. These investigators reported that leukocytes are an essential prerequisite to corneal vascularization since they produce one or more factors which stimulate vascular growth. Whether these factors are specific stimulators of neo-vascularization or are the result of proteolytic activity of collagenases, neutral proteases or cathepsins released by the leukocytes is not as yet clear. Work is in progress to elucidate these parameters.

In connection with cellular proteolytic activity, Kreger and Griffin[9] at the Bowman Gray School of Medicine, have shown that extracellular proteases produced by Serratia marcescens, a bacterium capable of producing significant infections in many human tissues and organs, can cause rapid and extensive damage to the rabbit cornea.

Berman, Gordon, Garcia and Gage[10], at the Eye Research Institute of Retina Foundation in Boston, have continued to clarify the role of certain proteins on corneal collagenase activity. They found that a protein in the human serum, alpha 2-macroglobulin, inhibits corneal collagenases by the formation of tight complexes with them and developed a method by which tears can be examined immunochemically for the presence of collagenase.

The work of Fromer, Kreger and Berman is important for understanding corneal pathology in apparently disparate situations, e.g. corneal vascularization, graft rejection and vascularization due to alkali burns. All these corneal pathological entities have in common excessive proteolytic activity. Studies of the activation, inhibition, and regulation of these enzymes are vital to improving treatment of corneal pathology.

Santamaria and Manski[11] at Columbia University developed a laboratory animal model for experimental studies of corneal healing in certain collagen-vascular diseases. The healing of the cornea frequently is poor or delayed in those diseases in which collagen and vascular tissues are affected. Santamaria and Manski were able to induce adjuvant arthritis experimentally in laboratory animals which had undergone corneal transplantation. These investigators reported a disruption of healing in the corneal transplants in animals with arthritis as compared to normal animals.

Polack[12] at the University of Florida has studied the anatomical and functional changes which occur at the corneal host-graft junction. Using light, transmission, scanning electron microscopy and autoradiography, he studied the morphology and repopulation of the cells in the scar, and reported that 50% of the cells present come from the host and are fully functional. Polack also made important observations on the suturing of the graft and noted that very tight (continuous) 10-0 nylon sutures produce necrosis of the edge of the wound and delay healing.

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CATARACT

INTRODUCTION

The human lens is a delicate system of proteins, nucleic acid and small molecules, harmoniously integrated as the lens undergoes the process of growth and maturation. Since there are no blood vessels or nerves within its structure, the lens is amenable for a disparate number of studies. However, the main goal of research performed by many investigators in the past year was further elucidation of the changes which occur during cataract formation in the protein structure and metabolism of the lens.

AGGREGATION OF LENS PROTEINS AND THE DEVELOPMENT OF SENILE CATARACT

It is well-established that one of the causes of senile cataract is a progressive structural change of the lens proteins characterized by high molecular weight aggregates in the central region of the lens. These protein aggregates are held together by covalent linkages and weak non-covalent bonds. With aging, the percent of covalent bonding appears to increase. Due to its anatomical structure and growth pattern, the lens is unable to repair or modify the insult or damage to its proteins that accompanies the process of aging. As a result, degraded protein molecules accumulate and an opacity or cataract develops.

The relationship of the high molecular weight proteins to another fraction of protein in cataract that is insoluble had been clarified in Spector's[1] laboratory at Columbia University. It is now clear that there is a transformation from low molecular weight protein aggregates to increasingly large protein aggregates and insoluble protein. The same population of polypeptides appear to be associated with this spectrum of increasingly larger aggregates. Of particular interest is the appearance of atypical degraded polypeptides not found in normal younger lenses. An unusual 11,000 dalton polypeptide appears to be one of the major constituents of these giant aggregates. This observation by Roy and Spector[2] suggests that cleavage of polypeptide linkages may also be involved in the aggregation process.

Another characteristic of the aging lens is that it becomes increasingly yellow. This yellowing is found in the high molecular weight protein aggregates, some of which appear to become insoluble. Dillan, Spector and Nakanishi[3] have found that the yellow components are associated with an atypical fluorescence. One of the fluorescent components has been isolated and shown to be a beta carboline. This compound arises from a normal constituent of the lens protein and may be one of the cross-linking agents involved in the formation of the high molecular weight protein aggregates. This is the first time such a component has been defined in the lens.

Another development in Spector's laboratory[4] is the delineation of the effect of aging on a particular human lens protein, alpha crystallin. This work indicates that cleavage of the polypeptides as well as other significant changes in chemistry occur.

Jedziniak, Kinoshita, Yates and Benedek[5] at the Massachusetts Institute of Technology and the National Eye Institute have measured the concentration of heavy molecular weight protein aggregates (HM) in normal human lenses ranging in age from 5 to 62 years, and established the distribution of HM component in human sclerotic cataracts. Their results show that the concentration of HM rises with lens age (increasing by a factor of 10 between ages 20 and 62) and occurs primarily in the nuclear region of nuclear sclerotic cataractous lens. The increase is quite striking after the age of 20. These large proteins are of sufficient size and quantity to become light-scattering centers and thus may be responsible for the opacification of these lenses.

On the basis of the theory of light scattering, Dr. Benedek proposed in 1971 that opacification of the lens in cataract is produced by the spatial fluctuations in the index of refraction of the protein-water system in the lens. In particular, these spatial fluctuations were proposed to be in the form of heavy molecular weight aggregates of lens proteins. Since Spector and Jedziniak have observed heavy molecular weight lens protein aggregates only in solutions, it was reasonable to inquire whether these aggregates are a product of the biochemical separation or indeed whether the aggregates exist in the intact lens itself.

Using the technique of optical mixing spectroscopy, Tanaka and Benedek[6] at MIT have observed high molecular weight aggregates in intact human and bovine lenses, confirming the finding of Spector and Jedziniak. The technique developed by Tanaka and Benedek is potentially a very useful tool for studyng the efficacy of medical treatment for cataract as well as for following the natural history of senile cataract. The investigators are now exploring whether their technique can be applied safely to the study of human lens proteins in vivo.

The use of Raman spectroscopy is a new application of a physical method to study intact lenses. This technique provides information about the tertiary structure of the proteins in the crystalline lens. While the optical mixing spectroscopy developed by Dr. Benedek allows one to observe lens proteins only in their entirety, Raman spectroscopy can detect subtle changes in a segment of a protein. Kuck, East and Yu at Emory University[7] and the Georgia Institute of Technology have applied Raman spectrosocpy successfully in intact, capsulated living avian lens and reported that, in contrast with the bovine lens proteins, the avian proteins have an alpha-helical configuration. The occurrence of low thiol protein in the alpha-helical form may explain the failure of the avian lens to develop cold cataract or a firm nucleus. The importance of the Raman spectroscopy is that it be used to detect in vivo molecular changes in the proteins.

CELL BIOLOGY OF THE LENS

One of the unsolved problems in biology is the mechanism(s) which control the initiation of cell division. Investigations on the nature of cell division indicate that environmental factors play a role in determining

whether or not cells enter mitosis. Of the numerous environmental factors that trigger mitosis, attention has recently focused upon serum factors with insulin-like activity.

The lens is an ideal tissue for studies of the factors which control cell division. It is avascular, not innervated and is enclosed within a limiting membrane. A number of efforts have been made to gain a better understanding of the mechanism which controls the initiation of cell division in the lens by Reddan, Unakar, Harding, Bagghi and Saldana[8] at Oakland University. Reddan has shown that insulin could affect the induction of mitosis in lens epithelium. This work indicates factors which influence lens development and lens wound repair, and since insulin induces cell division, it has some practical application in maintenance of the lens for in vitro studies.

The work of Eisenberg and Rae[9] at the University of Texas on the bioelectric properties of lens cells, has shown that individual lens fibers are not independent, as was postulated in the past, but are functionally interconnected to adjacent fibers. By applying electric current to one of the lens fibers, Eisenberg and Rae have demonstrated that the current readily flows into contiguous fibers. Since lens fibers, unlike nerve and muscle cells, do not themselves produce electrical impulses, it is unlikely that the ability of electric current to move from lens cell to lens cell is itself physiologically important. Rather, the electric current experiments simply allows one to measure the cell-to-cell pathways.

The studies of Eisenberg and Rae have also shown that certain low molecular weight dyes (Procion), placed into single lens fibers through a small glass microelectrode, are free to move from one fiber to another. Although the functional importance of this cell-to-cell movement of low molecular weight compounds cannot be stated with certainty at present, it seems reasonable to assume that the cell-to-cell pathways might allow equilibration of metabolites within the avascular lens. Such pathways might also allow the anterior epithelium of the lens, through its active transport processes, to help regulate the chemical content of cells deeper in the lens.

Cotlier, Baskin and Kresca[10] at the University of Illinois reported that a naturally occurring phospholipid (lysophosphatidyl choline) LPC in the aqueous humor affects sodium ion and water transport into the lens. By injecting an enzyme (phospholipase A) PA, which generates the LPC in the vitreous humor, these investigators were able to induce posterior subcapsular cataract in rabbits. The results indicate that the integrity of the lens membrane becomes compromised if the concentration ratio LPC phosphatidyl/choline + cholesterol is abnormal.

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GLAUCOMA

INTRODUCTION

The term glaucoma designates a group of debilitating eye diseases. It is one of the leading causes of visual impairment accounting for approximately 12 percent of all cases of blindness in the United States. Whereas its onset typically takes place in middle to older age groups, its occurrence is often unpredictable. Because glaucoma is usually asymptomatic, it may result in considerable irreversible damage to the eye prior to diagnosis and treatment.

The intraocular pressure in the anterior chamber of the eye is normally maintained by the production and secretion of aqueous humor by the ciliary body and its outflow via the trabecular meshwork and Schlemm's canal to the venous circulation. Normal intraocular pressure is clinically measured within the range of 14-20 mm Hg.

Although elevation of intraocular pressure does not always indicate the onset of glaucoma, it is generally accepted that patients with glaucoma are more likely to have significantly higher intraocular pressures than non-glaucomatous individuals. Highly elevated intraocular pressure, particularly when sustained over extended periods of time and accompanied by optic disc cupping and damage to the optic nerve head, causes loss of vision in various parts of the visual field. As the disease progresses these areas of visual loss increase in size, visual acuity progressively worsens, objects may appear broken or only partly seen, direct vision is lost, and the individual becomes unable to cope with the external world through the sensory modality upon which he or she has learned to be most dependent.

In angle closure glaucoma, the aqueous outflow route is obstructed due to a shallow anterior chamber and/or iris-lens positioning, e.g., by apposition of the iris with the openings in the trabecular meshwork. Intraocular pressure thus increases as the normal outflow passage is partially interrupted. On the other hand, in primary open-angle glaucoma, the most prevalent form of the disease, there generally is no obvious obstruction of the trabecular meshwork. There is evidence, however, that outflow facility typically is reduced in cases of primary open-angle glaucoma. The full explanation of the causes of primary open-angle glaucoma has yet to be established.

In the above and most all other categories of the glaucomas (e.g., congenital and various secondary or combined cases), the primary concern is with neural damage caused by, or occurring in conjunction with, sustained, abnormally high intraocular pressure. Increased optic disc depression or cupping also may correspond with this damage. As nerve fiber damage progresses, there is subsequent degeneration and atrophy of the retina and optic nerve.

Since its creation as one of the National Institutes of Health, the National Eye Institute (NEI) has supported research aimed at combating glaucoma. The principal efforts have been geared toward: investigating pressure changes of the aqueous humor; earlier detection; more reliable, accurate, and complete diagnosis; new and improved modes of treatment, prevention and cure;

and support for relevant fundamental research from which the above clinical applications ultimately develop.

ETIOLOGY AND MODES OF TREATMENT FOR GLAUCOMA

For many years the Glaucoma Clinical Research Center at Washington University under the direction of Dr. Bernard Becker has conducted a series of clinical studies with glaucoma patients. A large population of well-defined patients has been recruited, and they participate in various studies which are oriented not only toward management of the disease and treatment but also toward improving early diagnosis.

Corticosteroid drugs have been of particular interest to Becker and his associates. Corticosteroids have become important in glaucoma research because topical use has been found to induce ocular hypertension characteristics similar to those found in primary open-angle glaucoma. The Washington University group, along with others, has studied the intraocular pressure response to topical corticosteroids. Three responder groups had previously been identified: low responders (NN); intermediate responders (NG); and high responders (GG).

Palmberg, Mandell, Wilensky, Podos, and Becker[1] recently published results on the reproducibility of topical testing using the corticosteroid dexamethasone. The data show that responses were similar for all three response groups when the same eye was tested at two different times (71% for NN; 74% for NG; and 79% for GG). Responses from the contralateral eye when not treated showed no effect.

In other studies at Washington University, Cantrill, Waltman, Palmberg, Zink and Becker[2] and Cantrill, Palmberg, Zink, Waltman, Podos and Becker[3], have established dose response curves in primary open-angle glaucoma patients for inhibition of lymphocyte transformation by various corticosteroids. In vitro potency of the drug was found to be dissociated or independent of intraocular pressure changes. This may suggest differences in the relative action or ocular penetration of the drugs.

Other glaucoma patient categories have been investigated for corticosteroid response. One of these is pigmentary glaucoma, which is said to be an open-angle glaucoma with depigmentation of the iris and marked pigmentation of the trabecular meshwork. Pigmentary glaucoma patients were studied in comparison to NN, NG, and GG responders by Zink, Palmberg, Sugar, Sugar, Cantrill, Becker and Bigger[4]. The results indicate that, since the pigmentary glaucoma patient group did not show the same increased sensitivity to corticosteroids found with primary open-angle glaucoma patients, the two diseases may be etiologically separate entities.

Additional evidence that primary open-angle glaucoma is genetically different from other types of glaucoma has been presented by Kaufman and Kolker[5] from Washington University. In addition to comparing topical corticosteroid responsiveness, these investigators looked at aqueous humor dynamics, visual fields, optic discs, and anterior chamber angles in parents of primary congenital, or infantile glaucoma patients. The parents were studied

because the measurements are difficult to record in young children and also because the genetic link was of scientific concern. All parameters studied in the parents yielded values which did not differ from the general population. Therefore, a genetic relationship between congenital glaucoma and primary open-angle glaucoma was not established.

Probably the most widely used parasympathomimetic drug in the treatment of primary open-angle glaucoma is pilocarpine. However, questions about the clinical use of this drug remain to be answered. For example, because of limited penetration of the drug when topically applied and the need to maintain effective concentrations for long periods of time, it is important to determine what the best delivery vehicle is.

Rabbits were administered pilocarpine via five different vehicles by Green and Downs[6] in an investigation conducted at the Wilmer Institute of Johns Hopkins University. Compared to a saline solution used as a baseline control, Adsorbotears and 1% hydroxypropyl methylcellulose were found the most effective up to two hours after administration. Also, about 5 times more of the drug penetrated into the aqueous humor as compared to the saline solution.

In an extensive report by Spaeth[7] of the Wills Eye Hospital, 247 subjects were studied in a prospective investigation. The importance of fluorescein angiography as the major procedure to evaluate the vascular system of the fundus, particularly near the optic disc was demonstrated. The relationships between blood supply, intraocular pressure, and the optic disc cupping were considered in postulating mechanisms of visual loss in glaucoma.

Research with normal and congenital glaucoma patients is continuing at the University of California at San Francisco under Jocson[8]. Studies are being conducted on a relatively new surgical procedure: air trabeculotomy. This procedure, presently being performed on monkeys, employs a blast of air to puncture the trabecular meshwork. The developmental pathology of both the optic disc and the trabecular meshwork are significant in congenital glaucoma. When obstruction of the meshwork leads to buildup of pressure and progressive destruction, air trabeculotomy allows for the necessary surgery to be more easily performed with less tissue damage and a minimum of trauma. Over the past few years lasers have also been developed and refined for treating glaucoma as described by Worthen[9], University of California, San Diego. This procedure also has the advantages of mimimum tissue damage and pain, and often does not require extended recovery times.

INTRAOCULAR PRESSURE AND AQUEOUS HUMOR DYNAMICS

While the effects have not been fully established as being causal to glaucoma, the importance of maintaining intraocular pressure within normal limits has long been known and accepted. One of the primary areas of investigation along this line has been the interplay between aqueous humor production and secretion, and its outflow from the eye.

The ocular effects of catecholamines have been reviewed by Sears[10] at Yale University. Adrenergic effects on outflow and aqueous humor dynamics were suggested by Sears and Neufeld[11]. The relationship of these functions

to glaucoma is unknown and no evidence exists that adrenergic dysfunction gives rise to glaucomatous conditions.

The relationship of prostaglandins and the adrenergic system in the eye has been investigated by Neufeld and Page[12]. This work led to the development of a new model of the events at the adrenergic neuromuscular junction in the rabbit iris.

Aqueous humor outflow has been shown by Neufeld, Dueker, Vegge, and Sears[13] to increase with direct administration of cyclic AMP into the rabbit eye. In a more recent experiment with the monkey by Neufeld and Sears[14], similar procedures did not result in an increase in outflow facility. However, when a push-pull perfusion was employed, an increase in outflow facility similar to that observed in the rabbit eye was obtained.

GENETICS AND ANIMAL MODELS IN GLAUCOMA

The development of animal models of glaucoma is important in determining the hereditary characteristics of this group of diseases as well as making possible experiments which cannot be performed on humans. Once appropriate models have been developed, better controlled experimental investigations may be performed. Buphthalmic, albino, and albino buphthalmic rabbits have been described by Bennett, Bauer, Wu, and Kolker[15] of Northern Illinois University and Washington University.

Casey[16,17] of the University of California at San Francisco has previously described the prostaglandin-induced elevation of intraocular pressure using the rhesus monkey as a model. A new apparatus has recently been reported by Casey, Hart and Tarleton[18] which provides restraint to experimental monkeys and has been successful over extended periods of time for allowing better experimental controls in the administration of drugs to the eye.

Animal models can be of particular importance in glaucoma research, both for studying effects of various drugs and aqueous humor dynamics, and to trace the genetic factors in glaucoma. Such an animal model is being developed by Wyman[19] at Ohio State University. Results from water provocative tests outflow facility, intraocular pressure monitoring and the clinical appearance indicate that these animals may have a chronic simple type glaucoma rather than narrow angle or congenital glaucoma type.

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SENSORY AND MOTOR DISORDERS OF VISION

INTRODUCTION

The experience of sight is, in the final analysis, a result or outcome of the organized activity of the visual areas of the brain. Supported by the NEI, a large number of investigators with training in neuroanatomy, neurophysiology, neurochemistry and psychophysics continue to study the neurosensory processes that mediate vision in health and their abnormal function in visual disorders. They are also analyzing the reverse process whereby the brain controls the movements of the eyes in such a way as to optimize visual perception. Some of the most distressing malfunctions of the eye, such as strabismus and congenital nystagmus, and disorders of visual perception, such as amblyopia or dyslexia, are best conceived as disturbances in brain coordination between retinal processes and eye movement. Thus, research supported in the Sensory and Motor Disorders of Vision spans the concepts and techniques of the neural and visual sciences. Electrical recording from the brain, surgical procedures on extraocular musculature, administration of drugs, introspective determination of visual thresholds and behavioral training technology all can be found in one or another of the fundamental or clinical studies supported by the NEI program.

CONGENITAL,DEVELOPMENTAL AND DEGENERATIVE ABNORMALITIES

The discovery that albino rats and cats have abnormalities in the crossing of some of the sensory nerve pathways subserving vision has provided fascinating links between genes, pigment, anatomy and visual function in mammals. Lund, Lund and Wise[1], University of Washington, and Langer and Lund[2] of the same institution, are among the investigators who have pursued the abnormal projections from the retina to the lateral geniculate nucleus and to the superior colliculus in albino rats with electron microscopy and Golgi staining studies. In addition, Miller and Lund[3] have perfected in utero surgical techniques that can modify the growth of the retinotectal connections in the rat fetus. Damaging the superior colliculus on fetal day 15 (6 days before birth) with slit-like incisions can deflect the growing retinotectal axons, whether or not they belong to a genetically aberrant pathway. While the functional state of connections resulting from such surgical deflection is yet unknown, a potential has been demonstrated in this animal model for an early intervention to block or alter the anatomical expression of an aberrant gene.

Kaitz[4], working in the laboratory of Armington, Northeastern University, has studied the retention of visual function in the Royal College of Surgeons (RCS) strain of rats that undergo a congenital retinal degeneration. Under certain environmental regimes these animals were shown, by techniques of animal psychophysics in the Skinner box, to retain the ability to detect a visual warning signal, despite considerable retinal degeneration. Kaitz compared the visual function of dark-reared and cyclic-light exposed RCS rats to that of non-dystrophic animals. She found that subjects exposed to cyclic light and ones reared in the dark, both had nearly normal visual function in the given task. Subsequent exposure to continuous illumination, however, led to severe visual deficits in both sets of subjects. This work

bears on the feasibility of protective regimes--other than total light shielding--to maintain residual visual capacity in the congenital human retinal dystrophies.

Pachter, et al[5], New York University Medical Center, have made light microscope and EM studies of the extensor digitorum longus muscle of a strain of mice with a hereditary muscle dystrophy. The strain is said to be an animal model of myotonic dystrophy, a congenital human disorder that affects extraocular as well as other muscles. The investigators report central nucleation, atypical fiber diameter, fiber splitting and regions of focal fiber necrosis. Ultrathin 15 μm sections showed dilation of sarcoplasmic reticulum, mitochondrial conglomerates, sarcolemmal infolding and degeneration of myofibrils. Synaptic vesicles are distorted in shape and decreased in number. Thus both muscle fiber and motor end plate seem involved in the degeneration. Excessive numbers of axonal fibers, however, appear on hypertrophic fibers.

Tradition has it that the brain is irreversibly injured if deprived of blood flow for more than a few minutes. However, Lessell and Miller[6], Boston University School of Medicine, report that optic nerves and retinae of rhesus monkeys subjected to total circulatory arrest for 12-30 minutes do not appear to manifest demyelination or gliosis. They state that the acute optic neuropathy of shock seems to occur only with hemorrhage.

A 1975 Annual Report dwelt on research into the bases of functional amblyopia in the developing nervous system. Sherman, et al[7], University of Virginia, continue to demonstrate the special vulnerability of the lateral geniculate nucleus (LGN) to imbalances of visual input from the two eyes. In the LGN of kittens reared from birth with the lids of one eye sutured, cells of the Y-type are greatly reduced in number in the binocular segment within which the central portion of the visual field is mapped. The anatomical damage appears to result from interference with a process of binocular competition in normal development. Von Noorden and co-workers[8], Baylor College of Medicine, are concentrating, among other problems, on the reversibility of the neuroanatomical changes produced by patching or lid-suture.

OCULOMOTOR DISORDERS

A. Control of Eye Movement

Robinson[9], Wilmer Ophthalmological Institute, Johns Hopkins University, has presented by way of a control system model, a synthesis of the voluminous electrophysiological and mechanical data now available on ocular pursuit movements, saccades and gaze stabilization. He begins with a linear differential equation which relates eye position and velocity to motorneuron discharge rate. He then considers the generation of the neuronal signals necessary to produce the known kinds of eye movement. The feedback control circuit scheme posits the presence of a "final common integrator" that combines vestibular and retinal influences to generate the required control signal. Robinson marshals evidence to suggest that the integrator is in the paramedian positive reticular formation. One

function of the cerebellum may be, according to Robinson, a "parametric adaptive" action, that is adjustment of the gains in the various optomotor feedback loops in such a way as to compensate reflex imbalances and "repair" oculomotor malfunctions. Among these may be the various saccadic and vestibuloocular dysmetrias. Robinson's model of adaptive oculomotor control links interestingly with more general theories of cerebellar function, with possible application to neuroophthalmological diagnosis.

B. Strabismus

Metz et al[10], Smith-Kettlewell Institute for Visual Sciences, Pacific University, have employed new electromyographic techniques at the time of surgery for a "quantitative diagnosis" of the condition of the extraocular muscles. They report that in patients with Duane's retraction syndrome medial rectus activity remains normal, while the lateral rectus fails to recruit. Paradoxical innervation phenomena also are revealed by the technique in the abnormal lateral rectus.

VISUAL SENSORY AND PERCEPTUAL DISORDERS

A. The New Psychophysics

The idea that the perception of visual pattern is mediated by distinct neural "channels," each "tuned" to a band of spatial frequencies--a concept suggested by advances in image-processing technology--has stimulated much recent research in psychophysics as well as neurophysiology. What has been called a spatial Fourier analyzer theory of pattern perception has led to the replacement of traditional test stimuli in the laboratory, such as dots or pairs of lines or letters, by sinusoidally-modulated gratings or checker board patterns. The reason is that the traditional test patterns, elementary though they may seem, turn out to be quite complex if mathematically analyzed into their Fourier spectrum of spatial frequencies, while the less familiar sinusoidal grating is in fact mathematically elementary. These new test materials are often generated visually by computer or electronically controlled displays. And the rather sophisticated mathematics of integral transformations and orthogonal functions plays an increasing role not only in the analysis of data but in the very design of the psychophysical experiment.

In this spirit, Kelly and Magnuski[11], Stanford Research Institute, have compared the contrast threshold vs. spatial frequency curves generated by observers exposed to a) rectilinear sine wave, b) circular sine-wave, and c) circular Bessel function target gratings. These targets differ in the space domain by such local features as circularity or lack of it, and contrast uniformity or lack of it. They also differ in their (two-dimensional) spatial Fourier spectra. On the basis of their data the investigators conclude that it is the targets' spatial spectral composition, specifically the magnitude of the principal component, which governs their detectability, rather than any stimulus domain feature, such as local contrast. Their conclusions are buttressed by similar findings with checkerboard patterns.

Westheimer[12], University of California, Berkeley,has considered the problems encountered in accounting for the hyper or vernier acuities on the basis of the spatial distribution of receptor cells on the retina. He argues that only multiple parallel processing mechanisms, each abstracting different aspects of the stimulus' information content, can explain vernier acuities that survive the degradation of the retinal receptor apparatus in disease or aging. Among the parallel processing models Westheimer has examined is the idea that each channel is tuned to a band of Fourier frequencies. In particular, he has compared the spatial Fourier transforms of sub- and suprathreshold vernier test stimuli in an effort to determine whether the model can reasonably account for the observed acuities.

Also working on the hypothesis of tuned channels in human vision, Smith[13], University of New Hampshire, reports that retinal disparity and motion of the stimulus must be considered along with target spatial frequency. Thus it appears that the appealing simplicity of the Fourier analyzer model of pattern perception will have to yield to substantial modifications.

B. Neural Mechanisms

The classical limulus (horseshoe crab) preparation continues to provide insights into the operation of visual systems that bear on the perception of higher animals, including man. Barlow, Institute for Sensory Research, Syracuse University, and Quarles[14], IBM, Thomas J. Watson Research Center, have studied spatial contrast effects in the optic nerve of the horseshoe crab's lateral eye that correspond in some ways to the enhanced light and dark bands that appear at the edge of a shadow in human vision, the so-called "Mach bands." The "bands" observed by Barlow and Quarles consist of enhanced differences in steady-state firing rates on the part of fibers corresponding to retinal elements close to the border formed by a spatial step-function of illumination impressed on the crab's array of ommatidia. The enhancement in question is the result of inhibitory interactions between retinal elements. Barlow and Quarles have been able to test quantitative models against their data by computer simulation. A deviation from the Hartline-Ratliff equations for steady-state activity appears, because of an inhibitory nonlinearity, attributable to a dependence of the sensitivity of the receptor to inhibition on the level of incident illumination[15]. Further, second-order damped spatial oscillations of firing rate appear between the primary maxima and minima of the "Mach bands." Barlow and Quarles attribute these second order effects to recurrent inhibition. These experiments carry to the level of fine quantitative details the effort to locate the physiological basis of a perceptual phenomenon.

Habituation, i.e. response decrement following repeated presentation of the same stimulus, is primarily a behavioral concept. Appropriately or not, however, it has been invoked for the decrease in neuronal firing rate seen in sensory pathways upon multiple exposure to stimuli. Oyster and Takahashi[16], School of Optometry and Medical Center, University of Alabama, Birmingham, have studied the responses of superior colliculus neurons in the rabbit to repeated stimuli, controlling for stimulus parameters, eye movement or drift and the receptive field properties of the neurons examined. In particular, they tested for the possibility of habituation where the stimulus had optimal "trigger" properties, where cell

response properties were determined and where eye movements were not present. Both habituating and non-habituating cells were found. Most collicular cells which did not habituate had the property of weak or absent surround inhibition, but responded well to spots or moving targets. Cells which habituated did not respond to spots but were direction-selective and possessed strong inhibitory surround properties. Oyster and Takahashi suggest that habituation phenomena at the single-cell level may be associated with strong inhibitory inputs. However, many other factors including the frequency of the stimulus trains used, play a role in the presence or absence of response decrements.

The supersedence of qualitative methods of analysis by quantitative ones in morphological studies of the structure and connectivity of nerve cells has been impeded by great difficulties in data collection. Neural processes must be analyzed in three dimensions, a very large number of observations must be made, and staining failure and artifact must be considered. Cowan, et al[17,18], Washington University, St. Louis, have reported on a computer analysis of Golgi-impregnated neurons by means of a semi-automatic system for collecting data on the dendritic branching and dimensions of cerebellar and cortical neurons. Stepping motors position and move the slide displayed to the microscope according to the commands of controls manipulated by the operator. On the basis of 'identifiers' provided by the operator, a computer-linked TV camera samples data points on the slide, computes the lengths of dendrites and their segments, and orders them into appropriate sets that reflect the branching structure. These data are then stored for further statistical processing and an image of the reconstructed neuron displayed on the computer CRT. The reconstruction can be rotated so as to provide views of the dendritic tree from several different aspects. The system is also capable of counting silver grains in autoradiographs[19]. Grains over sections up to a density of 300-500 grains/sq. μm can be counted. Since axonal connections are now traced autoradiographically, the automated counting of silver grains (whose number is directly related to the amount of radioactivity) constitutes a great technical advance.

Kalaha-Brunst, Giolli and Creel[20], Veterans Administration Hospital, Phoenix, Arizona, report an improved silver impregnation method for tracing degenerating nerve fibers and their terminals in frozen section. An acidified, weakly alcoholic solution of Mayer's hemalum is used. A superior selective impregnation of degenerating nerve fibers is obtained. The method has been successful in demonstrating degenerating cortico-cortical fibers.

ELECTROPHYSIOLOGICAL TECHNIQUES APPLICABLE TO MAN

Kelly[21], Stanford Research Institute, reports a new method for stabilizing images on the retina. By interfacing a CRT stimulator[22] and the Purkinje eyetracker[23], a feedback loop is created whereby the stimulus pattern on the CRT screen moves to compensate for any eye movement. The gain of the loop is adjusted to unity by setting to a criterion of rapid subjective fading of the image. The system matches older image-stabilizing systems, in accuracy, without requiring contact lens fitting.

In a related development, Crane[24], Stanford Research Institute, has combined an eyetracker and optometer to create an instrument that simultaneously and accurately measures the instantaneous refractive power of the eye and the instantaneous direction of gaze. This three-dimensional eye tracker is meant to compare the operation of voluntary and involuntary systems for accommodation and to determine the portions of the retina that are sensitive to accommodative stimuli.

REHABILITATION

Saunders[25] has reported on a variety of electrocutaneous displays being developed by an interdisciplinary team at the Smith-Kettlewell Institute for the Visual Sciences, Pacific University, to circumvent some of the handicaps of the blind. In one tactile television system, images from a head-mounted TV camera are displayed on the abdomen by means of a matrix of 256 electrotactile stimulators. Concentric electrodes are used to limit surface current spread, confining each stimulated area to a few square millimeters of skin. An essential requirement is capacitive coupling to prevent any net DC flow. The sensations produced are acceptable. The skin, therefore, can serve, to a limited degree, as a substitute for the retina for the reception of information about the configuration of the immediate environment or of patterned educational materials.

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INTRAMURAL RESEARCH

ANNUAL REPORT
NATIONAL EYE INSTITUTE
July 1, 1975 - June 30, 1976

REPORT OF THE CLINICAL DIRECTOR

Elmer J. Ballintine, M.D.

The primary mission of the NEI Clinical Branch is to conduct research related to those aspects of ocular disease which can be studied best in man. Such investigations must meet the same standards of scientific rigor and validity that apply to other biologic experiments and do so within the ethical and humanitarian constraints imposed by the fact that the subjects are people.

Each research plan is reviewed by a protocol review committee composed of representatives from the Clinical Branch, other parts of the NEI and NIH, and others who are not employees of NIH. The protocol may also be reviewed by the Clinical Review Committee of the Clinical Center's Medical Board. These reviews help assure that adequate safeguards for rights and welfare of patients are maintained and that patients are fully informed about both risks and potential benefits of their participation. Patients are accepted only if referred by an ophthalmologist outside the Institute and only if the patient's condition is appropriate for study in an approved protocol.

In the past few years the randomized controlled clinical trial has been recognized as the most reliable way to test a variety of medical hypotheses. The success of several of these trials, such as the Diabetic Retinopathy Study, has depended on the cooperation of a number of participating institutions. They have required detailed protocols, organizations to insure uniformity and reproducibility of procedures and data collection, complex methods for randomization, "masking" of patients and observers, and other precautions against bias.

One of the objectives of the Clinical Branch is to demonstrate that rigorous clinical trials of important medical hypotheses can also be performed within a single institution with a staff of modest size. One example is the Clinical Branch's Urokinase Central Retinal Vein Occlusion trial conducted by Kollarits et al. In this study, patients with occlusion of the central retinal vein are randomly assigned to treatment with either heparin, urokinase, or conservative treatment. Both patient and examiners are "masked" so that the treatment assignment is not known when the posttreatment examinations are performed. Admission of the first four patients to the study has demonstrated that it is practical. Recruitment of patients is continuing.

Formal protocols incorporating these principles either were in operation in FY 1976 or were being reviewed. These protocols have been used for testing surgical procedures for relief of hemorrhagic glaucoma, surgical procedures for treatment of glaucoma after multiple surgical failures, irrigating solutions for use in vitrectomy and the effectiveness of early treatment of vitrectomy, and the effectiveness of early treatment of ocular hypertension in preventing progression to chronic simple glaucoma.

The dominant concern of the scientists in the laboratories of the Clinical Branch is the study of manifestations of human eye disease. These studies may require extensive development of methods and demonstration of biochemical or physiological mechanisms as preliminaries to their application in patients.

For example, the Q-switched laser can be used to open passages through the trabecular meshwork which may remain open for at least a few months. In anticipation of a trial in glaucoma patients, a Q-switched laser has been installed, and the details of its use are being worked out by Gaasterland and Kupfer, who are treating the eyes of monkeys.

In monkey eyes, treatment of the trabecular meshwork with argon laser can be manipulated to produce a mild chronic elevation of intraocular pressure. A cupping of the optic disc over a period of several months develops, which closely resembles that of simple glaucoma. The relationship of this cupping to changes in axoplasmic flow of retinal ganglion cells has been studied. The work will be extended to study the alterations in optic disc blood flow using diffusible indicators.

The mechanisms by which drugs influence the rate of production of aqueous humor were studied by Macri and associates using isolated perfused cat eyes and monkey eyes in vivo.[1,2,3]

The results of these experiments indicated that an important action of acetazolamide is the reduction of aqueous humor production by vasoconstriction of the blood supply of the ciliary process and that this reduction is prevented by phencyclidene. Since phencyclidene has no effect on the carbonic anhydrase inhibition of acetazolamide, the vasoconstrictive action of acetazolamide is not carbonic anhydrase-related.

The results support the idea that aqueous humor formation is regulated by the tonus of two sets of vasoconstrictive mechanisms, one acting on afferent and the other on efferent blood vessels of the ciliary processes.

Other laboratory investigations by Ballintine, Buzney, and Weiblinger used material obtained from surgical, autopsy, or blood specimens. Surgical specimens from patients undergoing trabeculectomy furnished samples of glaucomatous trabecular meshwork for growth in tissue culture in an effort to discover a metabolic defect responsible for simple glaucoma.

Kupfer, Gaasterland, and Ross[4,5] continued their study of the parameters of the intraocular pressure of young and old normal volunteers and patients with glaucoma and ocular hypertension. The objective of their investigation is to evaluate the parameters of intraocular pressure in normal eyes, and eyes with ocular hypertension or glaucoma, before and after antiglaucoma medication. Seven parameters are determined before and after medication: intraocular pressure, episcleral venous pressure, total facility and true facility of outflow, pseudofacility, aqueous flow, and ocular rigidity. Calculations based upon data from this project indicate that in young volunteers, a substantial portion of aqueous formation occurs by ultrafiltration. In older volunteers secretion appears to be responsible for most of the formation of aqueous.

Study of such parameters more clearly defines the differences between normal and abnormal. The measurements can be extrapolated to more basic physiologic functions, yielding further insight into the function of the human eye.

The acquired data from a project conducted by Kupfer, Kuwabara, and Kaiser-Kupfer[6] which compares patients having pigmentary dispersion with and without glaucoma may enable NEI scientists to determine the risk of patients with pigment dispersion syndrome to develop glaucoma. Findings thus far have shown that patients may have pigment dispersion syndrome for as long as 15 years without developing glaucoma. There may be hereditary predisposition in some cases, as seen in the cases of a mother and daughter and two brothers. The steroid testing and PTC taste testing do not appear to show any particular categorization of these patients. It may become possible to identify which features of these determinations may have predictive value in forecasting which patients having pigmentary dispersion may develop a field defect. In addition, the relationship of pigmentary glaucoma to known characteristics of open-angle glaucoma will continue to be investigated.

A method was developed for isolating retinal capillaries by differential screening through nylon mesh by Buzney, Frank et al.[7] These capillaries, which are free of glial elements, from monkeys, bovine, and human autopsy retinas were grown in tissue culture. The mural cells grew preferentially. The presence of a "polyol pathway" which produced sorbitol in a medium that was high in glucose was demonstrated. This work will be extended to retinal capillaries from diabetic humans obtained at autopsy in an attempt to determine why mural cells disappear from the capillaries of retinas from diabetic patients.

The purpose of a project conducted by Frank and Coller,[8] which was terminated in June 1976, was twofold: to study the effects of argon laser photocoagulation as a therapeutic modality in certain retinal and choroidal diseases including background and proliferative diabetic retinopathy, retinal vein occlusion, sickle cell retinopathy, senile macular degeneration, the presumed ocular histoplasmosis syndrome, and idiopathic detachments of the retinal pigment epithelium; and to study the relationships between systemic levels of certain hematologic factors such as von Willenbrand factor, fibrinogen, and hemoglobin A_{1C}, and the rate of aggregation of normal donor platelets in the presence of plasma from test subjects together with adenosine diphosphate, and the presence and severity of retinopathy in individuals with longstanding insulin-dependent diabetes mellitus. While the nationwide Diabetic Retinopathy Study (DRS) has collected more voluminous data, this project has provided detailed information on visual fields and electrophysiological studies which were not covered by the DRS.

A study of factors influencing blood clotting mechanisms conducted by Frank and associates in patients with diabetes revealed that the von Willenbrand factor and plasma fibringen were consistently elevated, but in contrast to earlier reports by others, the platelet aggregation enhancing ability of plasma from the diabetic patients was not greater than that of plasma from matched normal volunteers. This observation casts doubt on the idea that aspirin may be used prophylactically against diabetic retinopathy by reducing a presumed increase in platelet aggregation.

In NEI's Laboratory of Vision Research, it has been demonstrated that retinal receptor cells contain two receptor proteins for vitamin A. While this work was underway, eyes were obtained at autopsy from a patient with retinitis pigmentosa who had been cared for in a study of retinal degenerative diseases conducted by Bergsma in collaboration with Chader and Whikehart of NEI's Laboratory of Vision Research. Isolation of vitamin A receptor proteins from the retinas of these eyes showed that the heavy molecular weight receptor was absent, while one of a normal amount of the low molecular weight was present. This is the first demonstration of a possible biochemical defect in retinitis pigmentosa related to vitamin A metabolism.

The objectives of another investigation, conducted by Bergsma,[9] are to improve the clinical classification of selective degenerative diseases of the retina and choroid and to provide a clinical resource for related laboratory investigations into the cause, prevention, and therapy of such diseases as retinitis pigmentosa and familial macular degeneration, as well as the effects of drugs toxic to the retina. Clinical studies have utilized specialized tests of such visual functions as dark adaptation, cone thresholds, and visual fields, electroretinography, electro-oculography, fundus photography, and fluorescein dye studies. During the course of these investigations, it has been determined that high dosage oral vitamin A therapy has no effect on the great majority of patients with pigmentary retinal degenerations. Nevertheless, most are helped by a combination of genetic counselling, discussion of prognosis, and advice regarding visual aids and rehabilitation. Related experiments in monkeys have shown that the subcellular damage to retinal cells produced by high doses of chloroquine occurs more than three years before electroretinography or fundus abnormalities are detectable.

In collaboration with the Experimental Pathology section of the NEI Laboratory of Vision Research, 234 eyes from the autopsy service of the Clinical Center were processed and examined histopathologically during the past year. Approximately 769 inpatient and 541 outpatient consultations were furnished for other Institutes at the Clinical Center. There were 1,280 outpatient visits during the year, 83 inpatient admissions, and 42 surgical operations.

The Clinical Branch continued to cooperate with other Institutes in the pursuit of unique research opportunities. The study of diabetic retinopathy among the Pima Indians in a project administered by the Epidemiology and Field Studies Branch of the National Institute of Arthritis, Metabolism, and Digestive Diseases was continued, as was the study of microangiopathy among patients with acromegaly. The study of ocular metastasis in National Cancer Institute patients undergoing treatment of breast carcinomas continued.

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ANNUAL REPORT
NATIONAL EYE INSTITUTE
July 1, 1975 - June 30, 1976

REPORT OF THE CHIEF, LABORATORY OF VISION RESEARCH
Jin H. Kinoshita, Ph.D.

During the past year, a reorganization of one of the sections of the Laboratory of Vision Research (LVR) took place. A new section on Retinal and Corneal Metabolism was created, and Dr. Gerald Chader was appointed its head. The investigators who were members of this section were originally in the Section on Biochemistry, the largest group of the Laboratory. The formation of this new section should improve the overall administration of the Laboratory. Moreover, it places a scientist with excellent administrative skills into a position of leadership.

One function of the Laboratory that may become a regular feature is the conduct of symposia which are initiated and organized by an LVR scientist and sponsored by the National Eye Institute. This past year a Symposium on the Pigment Epithelium and Its Relationship to the Retina in Health and Disease was conducted and chaired by Dr. Paul J. O'Brien. Participants, who came from various laboratories throughout the country, acclaimed the meeting as very successful. A publication of the proceedings will appear shortly in the journal Experimental Eye Research. Because this Symposium had such enthusiastic backing from the vision research community, another is planned. Dr. Toichiro Kuwabara will conduct a Symposium on Experimental Eye Pathology in October 1976. The sponsorship of these meetings is an important mechanism by which NEI intramural scientists can interact with those in the extramural community and join with them to make contributions to the advancement of a particular field of vision research. These symposia also help to fulfill the needs identified by the National Advisory Eye Council in its program planning report, which calls for gathering and disseminating important new knowledge in particular areas of vision research.

During the past year, LVR scientists received honors that further demonstrated the active participation and contribution by the Laboratory in the affairs of the overall vision research community. Dr. Peter Gouras returned from a year in Germany where he served as distinguished von Homboldt Scholar. Dr. Shuko Yoshikami was given the J. Arthur Rank Travel Award at the International Symposium of the Royal Society, London. Dr. Kinoshita served as Visiting Professor at McGill University and was invited as special lecturer by the 80th Congress of the Japanese Ophthalmological Society.

During the past year, many advances were achieved at the frontiers of the visual sciences. However, the glow of success was considerably diminished by two tragic events. We were deeply saddened by the deaths of Mrs. Jane Coulombre and Dr. Ludwig von Sallmann, who meant so much and who contributed so profoundly to the vision research field at the National Institutes of Health.

One of the most important investigations of the LVR during the past fiscal year was the study of the mechanism of cataract formation in experimental animals.[1,2,3,4,5] The objective of these investigations, which are conducted by Kinoshita and associates, is to explore possible means by which these cataracts can be prevented.

Because the enzyme aldose reductase appears to be involved in the process that initiates sugar cataract formation, efforts are being directed toward the discovery of more potent inhibitors of aldose reductase in hope of developing methods of preventing this type of cataract.

Studies have shown that flavonoids are potent inhibitors of aldose reductase, the enzyme which appears to initiate the formation of diabetic and galactosemic cataracts. These studies have been extended further to explore the feasibility of using these compounds for the prevention or delay of cataracts in intact diabetic animals. In the past, the difficulty associated with such experiments is the long time taken by most diabetic animals to develop frank lenticular opacity. We found that from this point of view, the Octogon degu, a South American rodent, is a convenient experimental model. It was observed that aldose reductase in the degu lens is higher than that of any other animal. The degu lens develops frank opacity as early as one week following the induction of diabetes by streptozotocin.

The administration of flavonoids to diabetic degus leads to a substantial reduction in the level of lens sorbitol as compared to controls. Preliminary experiments indicate that quercitrin is effective in actually delaying the appearance of opacity in diabetic degus, thus lending further support to the polyol theory of sugar cataract formation. These flavonoids do not appear to have any adverse effect on lens metabolism as indicated by lactate and ATP production and ion pump activity.

Work in the LVR by Chader, Wiggert, Bergsma, Helmsen, Robison et al. has also continued on the characterization of vitamin A receptors in ocular tissues.[6,7,8,9] Receptors have now been identified in retina and pigment epithelium of cow, pig, chick, monkey, and human. Differences between the receptor in retina and pigment epithelium in cow have been detected with regard to specificity for retinyl esters. A similar retinol receptor is also present in corneal epithelial and stromal preparations. This does not seem to be due to serum retinol-binding protein (RBP); the serum protein is not detected in monkey epithelium stroma as assessed by immunodiffusion techniques.

The retinas of several species also exhibit specific binding for vitamin A acid (retinoic acid). Although this receptor is of a size similar to the retinol receptor, it appears to be separate and distinct from the vitamin A alcohol binding species. It is interesting that the cytosol of bovine cornea does not contain a retinoic acid receptor.

The aim of another LVR project conducted by Helmsen, Wiggert, Bergsma, Chader et al. is (1) to determine how vitamin A (retinol) is transferred from

retinol-binding protein which is complexed with prealbumin in serum to the various layers of the cornea, and (2) to elucidate the chemical nature of the vitamin A receptors which reside in this connective tissue.

Specific receptors for retinol (alcohol form of vitamin A) but not retinoic acid (acid form of vitamin A) have been found in the cytosol of corneal epithelium derived from calf and cattle. The receptor migrates as a discrete peak of bound retinol in the 2S (approximately 20,000 M.W.) region in sucrose density gradients. As assessed by gel filtration the elution profile of the tissue is different from that observed with serum. After partial purification by gel filtration the tissue receptor complex was subjected to disc gel electrophoresis and was noted to migrate differently from retinol receptors present in serum. A limited number of higher affinity binding sites for retinol are present since incorporation of tritiated retinol into the epithelial receptor peak is markedly reduced by addition of excess non-radiolabelled vitamin A alcohol. The concentrated supernatant from pooled calf corneal stromas also exhibits a 2S receptor peak which is similar to that observed with corneal epithelium on sucrose density gradient centrifugation. Immunodiffusion studies performed with an antiserum which cross reacts with monkey serum retinol-binding protein failed to detect the presence of the serum protein in the cytosol of monkey corneal epithelium and the supernatant of pooled corneal stromas. Characterization to date in bovine and porcine tissues has demonstrated many similarities to the 2S tissue cytosol receptors previously demonstrated in retina and pigment epithelium.

In another LVR project, Shichi and associates have investigated basic as well as clinical problems that are considered of molecular-pharmacological importance for ocular function.[10,11] Major findings from this project are as follows: (1) The ocular aryl hydrocarbon hydroxylase induction occurs in responsive strains and under the same genetic regulation as the hepatic hydroxylase induction. (2) Culture conditions for chick embryonic pigmented epithelium have been established. (3) The aryl hydrocarbon hydroxylase activity can be induced in cultured chick pigmented epithelium with polycyclic hydrocarbons such as benz(a)anthracene. The result is interpreted as supporting our previous conclusion that aryl hydrocarbon hydroxylase induction in the mouse eye occurs in the pigmented epithelium. (4) All known mouse strains (e.g. C3H/HeJ, CBA/J, and C57/BL/6J 1e rd) which develop retinal degeneration belong to polycyclic hydrocarbon-responsive strains, a fact suggesting a possible correlation between aryl hydrocarbon hydroxylase induction and the onset of retinal degeneration. (5) Hydroxylated products of the aryl hydrocarbon hydroxylase reaction are found to labelize lysosomal membranes as measured by the release of acid phosphatase. (6) From these results, it is suggested that in genetically responsive mouse strains, release of hydrolytic enzymes from pigmented epithelial lysosomes would be enhanced by increased steady-state levels of phenolic products formed by the aryl hydrocarbon hydroxylase system and possibly may be of consequence in the process leading to retinal degeneration.

In another project, LVR investigators lead by Yoshikami have characterized the membrane topology and electrical currents of retinal visual cells and shown

that there must by a chemical transmitter involved in the initiation of sight.[12,13] These investigators have proposed that calcium is this transmitter and that its acceptance requires the fulfillment of three different tests.

1. Transient increase of intracellular Ca2+ in a visual cell should transiently shut down its dark current as light does.

2. Introduction of agents which stabilize Ca2+ intracellularly should affect the light sensitivity of the cell in predicted fashion.

3. Light should cause the visual cell internal Ca2+ to increase.

The first condition has been met and previously reported. The second test is being accomplished by putting membrane-impermeable calcium ion buffers into visual cells by the technique of fusing these cells with lipid vesicles filled with an appropriate buffer. That this technique is feasible has been shown with the use of a fluorescent dye, 6-carboxy-fluorescein. It clearly demonstrates that lipid vesicles can be used to introduce into the cell water space substances which are normally impermeable to membranes.

The Laboratory of Vision Research also investigated the anatomy and pathology of ocular tissues. Kuwabara and associates studied the effect of hyperosmotic agents on the ciliary epithelium.[14] Hyperosmotic agents (2M urea or 2M DL-lactamide), perfused into the interal carotid artery of rhesus monkeys, produced a marked decrease in intraocular pressure and an increase in aqueous humor protein. Fenestrae of the ciliary capillaries were broken immediately following the perfusion and the non-pigmented epithelium was separated from the pigmented epithelium. The pigmented epithelium, especially of the pars plana, then became degenerative. As intraocular pressure began to rise slowly, three to seven days after perfusion, the non-pigmented epithelium recovered to an almost normal structure, but the pigment epithelium did not regenerate. The surviving cells in the pars plicata formed the original apico-apical junctions.

The number of vacuoles in the endothelium of Schlemm's canal decreased while the intraocular pressure was low and increased gradually with the recovery of the intraocular pressure.

Another related investigation by Sakuragawa and Kuwabara studied the effect of AY-9944, trans-1, 4-bis (2-chlorobenzyl aminomethyl) cyclohexane dihydrochloride, an inhibitor of cholesterol biosynthesis, on the retina and optic nerve. Postnatally developing albino rats received daily intraperitoneal injection of 50mg AY-9944 per kg of body weight, and the animals were killed at various intervals ranging from three days to one month. The retina and optic nerve were studied by light and electron microscopy.

Shortly following the injection, lamellar inclusion bodies began to accumulate in ganglion, horizontal, Muller's, and pigment epithelial cells of the retina and in glia cells of the optic nerve. The inclusion bodies in some ganglion and optic nerve glia cells increased in size and number until they occupied the entire cytoplasm. The electron microscopic and histochemical

appearance of these inclusion bodies closely resemble those of abnormal sphingolipids in various storage diseases. Inclusion bodies in the pigment epithelium became crystalloid in appearance. Upon further poisoning, cells with the packed inclusion bodies began to undergo degeneration.

Development of myelin sheaths of the optic nerve was relatively well maintained under the intoxicated condition. However, prolonged poisoning resulted in marked degeneration of the optic nerve. The pathologic zone consisted of damaged axons and myelin sheaths and severely vacuolated glia cells. The degenerated lesions were eventually replaced by proliferated astrocytes.

The responses of neurons in the rod and cone systems of the cat retina were explored by Nelson, de Monasterio, Gouras et al. by means of intracellular electrodes and the Procion staining technique.[15,16,17,18,19,20,21] Horizontal cell bodies and cones had hyperpolarizing responses to light. The waveforms and intensity response characteristics of these units to red and blue monochromatic stimuli matched for either the rod or the cone pigment was suggestive of nearly equally mixed rod and cone inputs into these units. Thus, substantial rod input appeared to be injected into the cone system even at the cone photoreceptor level, and consequently was characteristic of the responses of horizontal cell bodies which were exclusively postsynaptic to cones. The half-saturating intensity of 441 nm stimuli for the rod input into cones and horizontal cells was about 400 quanta/μm^2/sec and about 160,000 quanta/μm^2/sec for the cone input. Little of this difference can be related to the different quantum catching abilities of rods and cones since the sizes of the rod and cone outer segments suggested that at 441 nm rods should have a collecting efficiency of .59 bleached rhodopsins/photoreceptor/incident quanta/μm^2, whereas cones, principally due to their longer wavelength photopigment, should have a collecting efficiency only slightly less: .16 bleached pigment molecules/photoreceptor/incident quanta/μm^2. Thus, in terms of bleaching rate of pigment rods were half saturated by about 240 bleaches/sec whereas cones were half saturated by about 25,000 bleaches/sec. This hundredfold difference in sensitivity between rods and cones in the cat retina is apparently related to differences in the neural interconnections of rods as compared to the neural connections of cones.

A continuous cable model has been invented to represent the responses of horizontal cells and cones, each of which on anatomical grounds is thought to form a kind of electrical syncytium, to slit stimuli of varying position and width.

In the rod system of the cat retina, horizontal cell axon terminals and rod bipolars were also found to hyperpolarize in response to light; however, these responses were dominated by rods with only a suggestion of irput from cones. The AII or "rod" amacrine cell has also been investigated. Its depolarizing responses are over 90 percent rod in origin and are accompanied by a quieting of baseline or synaptic noise. This evidence suggests that rod bipolars synapse onto rod amacrines with an inhibitory or sign inverting synapse.

The rod to rod bipolar, rod to horizontal cell axon terminal, and cone to horizontal cell body synapses, on the other hand, all appear to be excitatory.

In the last few months of the fiscal year, the LVR scientists initiated the study of intracellular responses of neurons of the macaque and rabbit retinas, both of which have color vision. Since the rabbit appears to be a dichromat having blue-(λ max 420-430 nm) and green-sensitive (λ max 500-510 nm) cones, we have given special emphasis to the study of the chromatic properties of the responses. We have found that opponent input from these cones mediates color-opponent responses of spike-generating neurons (probably ganglion cells), and that antagonistic concealed interactions between these cone inputs can be observed in S-potentials (which probably correspond to horizontal cell responses). These and other types of response also appear to receive rod input which has a spectral distribution very similar to that of the dominant input from green-sensitive cones. Sustained and transient hyperpolarizing and depolarizing responses have been recorded in the macaque retina. Cone and rod inputs have been found to mix in the responses of some inner nuclear layer cells (S-potentials); special attention is being given to the chromatic properties of these responses, since we have already recorded color-opponent S-potentials in the intact monkey. Presently, we are attempting intracellular stainings in both rabbit and macaque in order to anatomically identify the neurons.

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ANNUAL REPORT
NATIONAL EYE INSTITUTE
July 1, 1975 - June 30, 1976

REPORT OF THE CHIEF, OFFICE OF BIOMETRY AND EPIDEMIOLOGY
Fred Ederer

During the year the staff of the Office continued its engagement in a wide variety of studies, including those to identify factors related to risk of eye disease, clinical trials to measure the comparative effectiveness of alternative methods of treatment, and research in statistical methodology. These involved both direct research activities by the staff and consultative assistance to others. The clinical trials program has grown with the start of a new multicenter clinical trial of vitrectomy in diabetic retinopathy. Efforts were continued in order to educate the medical research community in the problems of collaborative clinical trials.[1]

In July 1975 Harold A. Kahn, former Chief of the Office of Biometry and Epidemiology, retired and Frederick L. Ferris began a 3-year ophthalmology residency program at Johns Hopkins University. A new Section on Epidemiology was established in order to consolidate the various epidemiological activities other than clinical trials and natural history studies. Active recruitment for a Section Head is underway. In the early part of 1976, Philip L. Dern and Lawrence Rand joined the staff of the Office. The Steering Group of the Diabetic Retinopathy Vitrectomy Study has almost completed the Manual of Operations for the Study, and patient recruitment is expected to begin in the fall. Dr. Dern is serving as Project Officer for this Study. Dr. Rand is Special Assistant to the Diabetic Retinopathy Study Project Officer, Mr. Ederer, who was appointed to serve on the NIH Clinical Trials Committee.

Two of the major research efforts of the Office have produced their first results. The Diabetic Retinopathy Study recently found that photocoagulation treatment is beneficial to eyes in certain stages of the disease. This has necessitated some changes in the research protocol. These developments have been communicated to the scientific and general public.[2]

The Framingham Eye Study has produced its first findings and these have been submitted in the form of two research papers to the American Journal of Epidemiology. Dr. Roy Milton was appointed Project Officer for the Framingham Eye Study contract, replacing Harold Kahn.

The Office of Biometry and Epidemiology has been involved in additional research efforts related to clinical trials and diabetic retinopathy. Dr. Ferris and Charles McCarthy, Division of Research Services, have developed a standardized visual acuity measuring device for use in each of the 15 Diabetic Retinopathy Study clinics and in each of the 13 Diabetic Retinopathy Vitrectomy Study clinics. This system will help to assure uniform and constant illumination across specially prepared standard visual acuity charts.

Karen Yuen, of the Office, and Dr. M. Ray Mickey, UCLA, have developed a new statistical procedure for the comparison of two survival curves. This investigation in statistical methodology has direct application in clinical trials when comparing two treatments and where observations for each patient are time to failure or time to withdrawal. Dr. Yuen and Mr. Kahn, who is now working at Johns Hopkins University, have also prepared a paper for publication on the association of female hormones with blindness from diabetic retinopathy. The rates of blindness from diabetic retinopathy with or without other causes for persons in the Model Reporting Area (14 states) were determined and analyzed.[3]

Rita Hiller and Harold Kahn have prepared a paper for publication on senile cataract extraction and diabetes. This is an epidemiologic study of hospital discharge diagnoses using both national data and data from a local medical center.[4] Mrs. Hiller, other staff members of OBE and Dr. Matthew Davis, University of Wisconsin, are involved in a retrospective study to determine the prognosis for life in diabetics in relation to their severity of retinopathy.

The Section on Epidemiology was created during FY 1976. Mr. Ederer is Acting Head of this Section while a permanent Head is being recruited. The functions of the Section are to develop and conduct a program of epidemiological research in eye disease, with particular emphasis on diseases which cause blindness in the United States, to provide consultation on epidemiological problems to other vision research workers, and to provide training for vision research investigators in epidemiological methods. The epidemiological studies will emphasize investigations to uncover clues about etiology and pathogenesis, such as prevalence surveys, case control studies, population genetic studies, and studies directed at improving diagnostic methods.

An epidemiologic investigation into the association between average annual sunlight hours and the prevalence of cataracts was conducted by Mrs. Hiller and Dr. Yuen and Dr. Giacometti, ECP-NEI. The primary finding of this retrospective study is a positive association between the prevalence of cataract and residence in high sunshine areas.

Dr. Allen and Mrs. Helen Moorhead are reviewing the eye examination data from the National Health and Nutrition Survey. The purpose of this project is to determine the prevalence of visual disorders from the ophthalmological examination conducted on a random sample of the U.S. population participating in the National Health and Nutrition Survey, conducted by the HEW National Center for Health Statistics.

The Section on Mathematical Statistics and Computer Applications continued to engage in consulting, collaboration, and individual efforts in OBE, laboratory, and inter-institute studies involving applied statistics, methodological, and epidemiologic investigations. Dr. Milton visited India in order to support the beginning of field work by Dr. Arin Chatterjee, Christian Medical College, Ludhiana, for a cataract etiology study. He continued to consult with the NEI Clinical Branch, specifically with Dr. Douglas Gaasterland on studies of parameters of aqueous humor dynamics, and with Dr. Robert Frank on platelet aggregation and diabetic retinopathy.

Dr. Yuen assisted the NIH Division of Computer Resources and Technology (DCRT) by conducting two short courses on the characteristics and use of the UCLA BMDP statistical program system. Dr. Yuen collaborated with Dr. Thomas Wehr, Laboratory of Clinical Science, NIMH, and Mr. Howard Hoffman, Biometry Branch, NICHHD, in a time series analysis of circadian rhythm in a manic subject. She continued to participate in the statistical aspects of the NEI (Clinical Center) contract for a photogrammetric fundus camera.

Mrs. Hiller began preliminary discussion with Drs. Benjamin Hankey and Max Myers of the End Results Section, Biometry Branch, National Cancer Institute, concerning the use of the Connecticut Cancer Registry as a data source for studying malignant melanoma of the eye and retinoblastoma in terms of survival and association with other cancers. In collaboration with Dan Rosen, Director of Reports and Statistics Services, Department of Medicine and Surgery, Veterans Administration, Mrs. Hiller began investigating the possibilities for study of the assocciation of malignant neoplasms of the eye with other cancers or systemic diseases, using a diagnostically specified set of longitudinal patient records for FY 1969-1974.

Dr. Yuen continued her research work in statistical methodology: investigating the robustness of four sequential procedures against departures from normality and independence; investigating two non-parametric multi-sample location tests under heteroscodasticity; and investigating the small to moderate sample properties of the studentized Wilcoxon test for the Behrens-Fisher problem by Monte Carlo sampling. She is also involved in the design and development of statistical packaged programs for users of computers who wish to solve medical problems.

Dr. Mansour Armaly of George Washington University, and Mr. Dean Krueger, under the contract awarded to the Statistical Center of the Cooperative Glaucoma Study, have nearly completed the analysis of the Study's data. The results will be presented at the 1976 annual meeting of the American Academy of Ophthalmology and Otolaryngology.

Dr. Allen delivered several lectures on the principles of clinical trials and on epidemiologic methods in clinical research to students at Pennsylvania College of Optometry, Philadelphia.

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ANNUAL REPORT
NATIONAL EYE INSTITUTE
July 1, 1975 - June 30, 1976

REPORT OF THE CHIEF, OFFICE OF PROGRAM PLANNING AND SCIENTIFIC REPORTING

Julian M. Morris

In recognition of its expanded activities and dual responsibilities for program planning and scientific and public information, the NEI Information Office was elevated to Branch status during the year and re-designated the Office of Program Planning and Scientific Reporting.

PROGRAM PLANNING

The Office of Program Planning and Scientific Reporting intensified its support of the vision research program planning efforts of the National Advisory Eye Council. Coordination was provided for five meetings of the Council's Program Planning Subcommittee and for a total of seven meetings of the planning panels set up for each of the five NEI programs.

The Office provided the staff support necessary for the publication of the Council's 1976 interim report, Support for Vision Research. This 250-page report includes available data on support of research in vision and ophthalmology in the United States for Fiscal Year 1975. This compendium of active projects has provided the Subcommittee and panels with a valuable tool for their task of delineating the needs and opportunities in vision research. These will be published in the Council's second major planning document next spring.

A chapter of Support for Vision Research summarizes a report by Westat, Inc., an NEI contractor, which collected and evaluated existing data related to the extent and costs of eye disorders and blindness in the United States. The contract, which produced this Summary and Critique of Available Data on Prevalence and Economic and Social Costs of Visual Disorders and Disabilities, was managed by the Office.

Preparation of the NEI Annual Report was coordinated by this Office which also collaborated with personnel from other offices within the Institute to produce several evaluative and planning documents. The NEI section of the NIH Forward Plan for the Fiscal Years 1978 through 1982 was also prepared. This document concerns the mission, program balance, and strategy of the NEI, as well as current opportunities for progress in the five NEI research programs.

This Office, the designated focal point for evaluation activities within the Office of the Director, prepared the Institute's FY 1976 Evaluation Plan which includes proposals for use of set-aside NIH evaluation funds. This year, such funds will be used for partial support of the activities of the NAEC Program Planning Subcommittee.

The Office also answered requests relating to NEI planning activities from the House of Representatives, the Senate, and officials of DHEW and NIH. The Office responded to several requests for information from other Institutes at NIH regarding NEI program planning activities for use in developing their own research planning and prepared speeches concerning program planning for the Director, NEI. These include presentations to Congress; the Director, NIH; and several national associations related to vision and ophthalmology.

SCIENTIFIC REPORTING

The Office devoted major attention and resources this year to planning and disseminating scientific and public information on findings from the NEI-supported Diabetic Retinopathy Study (DRS). The Office also assumed primary responsibility for preparing and coordinating information about the new Diabetic Retinopathy Vitrectomy Study (DRVS) for patients, clinics, the mass media, and the general public. These activities required a large commitment of staff energy and hours and have been successfully implemented concomitant with meeting other demands and responsibilities.

Dissemination of Information on Clinical Trials

Diabetic Retinopathy Study--Commencing in January, the Office provided continuing guidance and assistance to NEI and DRS officials in preparing and executing a detailed timetable for implementing recommendations of the DRS advisory groups, which had concluded that sufficient data existed from the clinical trial to demonstrate a beneficial effect of photocoagulation at certain stages of retinopathy. The timetable included changing the Study protocol; notifying and reexamining patients; early publication of a scientific paper; and public announcement of Study findings. Regarding the latter, the Institute felt strongly that the DRS findings were so significant that widespread dissemination to the general public, as well as to the medical community, was both warranted and essential and in keeping with the high priority placed by NIH on rapid communication of research results. The Office therefore took extraordinary steps to publicize the information as broadly as possible.

These efforts included providing editorial assistance in the preparation of the scientific paper published in the American Journal of Ophthalmology and coordinating special arrangements with the Journal for obtaining a preprint of the article. The Office arranged for quantity printing and mailing of the preprint, along with a covering letter summarizing the findings, to more than 10,000 ophthalmologists and more than 3,000 physician members of the American Diabetes Association in this country. In addition, the Office provided assistance in preparing a letter to DRS patients explaining Study protocol changes and the significance of the findings.

Subsequently, the Institute held a press conference on the DRS findings on April 1, which was attended by 20 members of the major print and broadcast media. Advance copies of the research paper were distributed at the conference, along with a press release which was also issued nationwide. The Office also coordinated and facilitated local publicity with all DRS clinic coordinators and their institutions' public information offices.

These extensive efforts resulted in nationwide publicity. Stories were carried by approximately 150 newspapers, periodicals, and magazines; by the network CBS Morning News; the United Press International radio wire service; two Canadian radio networks; and by local television and radio stations across the country. Copies of the DRS press release were also sent to those members of Congress known for their interest in vision research and diabetes and three members placed material about the Study in the Congressional Record.

The Institute has had a very favorable reaction from members of Congress and Administration officials regarding the manner in which release of DRS research results was handled; some are understood to consider it as a model for dissemination of information about future clinical trials.

Prior to the release of these findings the Office wrote and supervised the production of a thirteen-minute film on the Diabetic Retinopathy Study (DRS). This film was incorporated into a DRS exhibit, also coordinated and produced by this Office, which was displayed at the annual meeting of the American Academy of Ophthalmology and Otolaryngology in Dallas. This exhibit won second prize among 50 ophthalmic exhibits, and an updated version including the new findings was presented at the American Diabetes Association convention in San Francisco. The film, which was loaned during the year to several groups interested in vision research or clinical trials, has subsequently been translated into Spanish for viewing by vision research scientists in Latin America.

Diabetic Retinopathy Vitrectomy Study--As it did in planning dissemination of information about DRS results, the Office provided guidance and editorial assistance to NEI and DRVS officials in announcing the second Study. This included assisting in the preparation of an editorial in AJO, as well as working closely with DRVS officials in developing the Study's patient explanation booklet and consent form. The Office again arranged for the preparation, printing, and mailing of letters to the same group of nearly 15,000 physicians, which informed them of the Study and called attention to the forthcoming editorial.

The Study was publicly announced by the Associate Director on May 9, in cooperation with a Research to Prevent Blindness, Inc., Science Writers Seminar, and by nationwide distribution of a press release. Thus far, approximately 75 stories have appeared in newspapers and periodicals throughout the country.

Subsequent to these efforts, other steps were taken to disseminate information concerning both clinical trials, including preparation of fact sheets for distribution to the public. For the Second Annual NIH Open House on May 1 and 2, the Office arranged with a manufacturer to borrow an argon laser, which was demonstrated by NEI physicians. The demonstration was complemented by a videotape from the press conference, which showed photocoagulation treatment and explained Study results. An exhibit aimed toward the general public, portraying photocoagulation and vitrectomy, was also displayed and the DRS film was shown both days of the Open House. This exhibit was also presented in early June at the Annual National Conference of the Juvenile Diabetes Foundation in New York. The Open House exhibit also provided visual acuity testing and included a sound slide show. A special case containing microsurgical instruments used in eye surgery was displayed adjacent to the photocoagulation and vitrectomy exhibit, mentioned earlier. The laser demonstration was covered by four local television stations. The Office also coordinated and assisted in presentations by to NEI participants in the Speakers' forum, held in Masur Auditorium.

Dissemination of information about these two clinical trials has required a considerable investment of Office time and resources but this investment has resulted in heightened public awareness of the Institute's commitment to the importance of rapid and broad communication of research results.

Special Activities

During the past year, the Office engaged in several activities of an unusual nature, ranging from Institute participation in Bicentennial events to participation in international efforts to call attention to preventable blindness.

The Office assisted the NIH Office of Communications in developing and coordinating exhibits which will be displayed throughout the Bicentennial Year at the new HEW South Portal Building in Washington and in a special science and technology exhibition at Cape Canaveral, Florida. This involved assisting in planning the exhibit concept; writing the script and having it recorded for a slide show depicting vision research advances; identifying and obtaining the appropriate slides from grantees; a question-and-answer series for a jukebox presentation on the 20 most commonly asked questions about vision and visual disorders; and a simulation of various kinds of impaired vision for children and adults.

The NEI, in cooperation with the NIH Fogarty International Center, hosted in November the first international conference concerning blindness prevention to be held at NIH. In connection with the conference, a meeting of international experts who serve on the Priorities and Projects Committee of the International Agency for the Prevention of Blindness, the Office issued a press announcement and a story for the NIH Record, arranged for a press conference at the National Press Club, and arranged for an interview on public radio with Sir John Wilson, founder and president of IAPB. The Office also prepared fact sheets on the six leading causes of worldwide, preventable blindness. The Institute Director serves as chairman of the Projects and Priorities Committee.

The Office, on behalf of the Institute, helped to coordinate U.S. observances and publicity on World Health Day, which this year highlighted the theme of prevention of blindness. A full-length feature article on the leading causes of preventable blindness was written by the Office and distributed by the NIH News & Features service to several hundred newspapers and science writers. A message was also drafted for the President, commemorating the anniversary of the World Health Organization and calling attention to the theme of preventable blindness.

The Institute was responsible this year for conducting the NIH Combined Federal Campaign and the Office accordingly assumed responsibility for supervision and coordination of special promotional events and publicity. The Office wrote, edited, or revised five stories for the NIH Record and prepared speech materials for use by the Director of NIH as well as for Drs. Kupfer and Raub.

Scientific Communications

The Office contributed five articles to the NIH annual publication, Research Advances, describing intramural and extramural research projects. The publication is to be distributed to medical schools and other grantee institutions in late summer of 1976.

In addition to disseminating information about scientific meetings, seminars, and workshops conducted by Institute staff, the Office also conducted tours of NEI facilities for visiting physicians, scientists, and a group of outstanding high school science students attending the Junior Science and Humanities Symposium.

The Office prepared a special publication on the Framingham Eye Study, which was distributed as a good will gesture to all Study participants and to the general public. A visiting Russian ophthalmologist was also interviewed about vision research advances in that country and an article was prepared for the NIH Record.

Consumer Education

The Office continued to expand its activities in the area of consumer education and communication, including drafting final revisions for a major HEW consumer publication on eye care. Four columns were written for Search for Health, which is distributed by the NIH Office of Communications to weekly newspapers across the country. The Office also wrote a number of radio spots, which have been taped by Dr. Muriel Kaiser, on vision and eye care. The spots are to be used by a large insurance corporation as consumer public service announcements. The Cataract booklet was updated with an insert on phacoemulsification and lens implants, with the inserts serving as position statements and informal fact sheets on these subjects. Similar material was prepared on orthokeratology, amblyopia, and vitreous floaters.

Press Relations

The Office responded to a record number of press inquiries (approximately 100) this year, due in large part to the good working relationships established at last year's Science Writers Seminar, and as a result of publicity about the DRS, DRVS, and IAPB meeting. In addition to two press conferences, the Office issued six press releases or announcements to the mass media, two to scientific journals, and prepared 13 articles for the NIH Record.

Requests for photographs and captions to illustrate newspaper and magazine articles, textbooks, entries in encyclopedias, and other specialized publications have increased severalfold. The demand has necessitated extensive efforts to locate, obtain, and maintain adequate quantities of suitable photographs.

Public Inquiries

Responding to written and telephone inquiries from the public continued to occupy a large portion of the time and effort of Office staff. Approximately 800 letters requiring detailed, reliable scientific information and 2,500 telephone inquiries of a similar nature were received during the year. Inquiries concerning cataract, glaucoma, and diabetic retinopathy continue to be most numerous.

The Office responded to 45 Congressional letters and other controlled correspondence and to 35 Congressional telephone inquiries. A growing number of inquiries are also being received from other government agencies; business,

professional, and scientific organizations; and publishers of encyclopedias and textbooks concerning statistics on eye disorders, facts on treatment, and current vision research efforts.

Publications

The Office distributed the following number of publications during the year:

Cataract	4,900	Retinal Detachment	1,650
Retinitis Pigmentosa	1,950	Corneal Diseases	1,780
Refractive Errors	3,750	Glaucoma	4,300
Diabetic Retinopathy	4,500	Macular Degeneration	1,700
Statistics on Blindness in the Model Reporting Area, 1969-1970			500
U.S. News and World Report, Interview with Dr. Kupfer			250
Evaluation of the Treatment of Diabetic Retinopathy, A Research Project, Reprint from the Sight Saving Review			1,300
Vision Research Program Planning			15,500
Support for Vision Research			2,000

Miscellaneous

The Office continued to provide background material for use in the legislative process, including opening statements, testimony, contributions to special reports on such topics as diabetes and transplantations, and detailed answers on specific questions submitted by members of Congress about visual disorders and treatment.

The Office prepared Presidential Messages for the World Health Organization, the Second World Congress on the Cornea, and provided assistance with the message for Save Your Vision Week.

As in the past, the Office coordinated the Institute's contributions to the NIH Report of Research Accomplishments, NIH Quarterly Communications Report to the White House, NIH Scientific Directory and Annual Bibliography, Freedom of Information Act Annual Report to the Congress, the Government Accounting Office Report, the Communications Plan, and the NIH Almanac.

As in previous years, the Office continued its liaison with various voluntary and professional organizations including the National Society for the Prevention of Blindness, Inc., Fight for Sight, Inc., American Foundation for the Blind, Inc., Research to Prevent Blindness, Inc., the Juvenile Diabetes Foundation, the American Diabetes Association, the American Association of Ophthalmology, the American Optometric Association, and the International Agency for the Prevention of Blindness.

Assistance was provided to the Director in the preparation of presentations before the American Academy of Ophthalmology and Otolaryngology, the Association for Research in Vision and Ophthalmology, and the International Congress on Ocular Trauma.

Clinical Branch

Ballintine, Elmer J., M.D.
- Aqueous Humor Formation in Monkey
- Ocular Hypertension Study
- Tissue Culture of Trabecular Meshwork

Bergsma, Donald R., M.D.
- Studies of Choroidal-Retinal Degenerative Diseases
- Studies of Ophthalmic Familial and Genetic Diseases

Buzney, Sheldon, M.D.
- In Vitro Studies of Retinal Capillaries

Christiansen, John M., M.D.
- The Pathogenesis of Abnormal Vascular Proliferations in the Vitreous

Cogan, David C., M.D.
- Quantitative Study of Clinical Eye Movement Abnormalities

Fishman, Martin L., M.D.
- Ultrastructural Demonstration of Calcium in Retina and Pigment Epithelium

Frank, Robert N., M.D.
- Biochemistry of Vertebrate Retinal Receptor Outer Segments
- Studies of Retinal and Choroidal Vascular Diseases

Gaasterland, Douglas E., M.D.
- Experimental Glaucoma in the Rhesus Monkey
- Laser Surgery for Glaucoma
- Radioiodinated Chloroquine Analog for Diagnosis of Ocular Melanoma
- Studies of Parameters of Intraocular Pressure

Gunkel, Ralph D., Ph.D.
- Research in Methods of Evaluating Visual Processes

Kaiser-Kupfer, Muriel, M.D.
- Ophthalmologic Screening for Metastatic Lesions to the Eye
- Pigmentary Dispersion With and Without Glaucoma

Clinical Branch (cont.)

Kollarits, Carol R., M.D.
- Application of Surgical Vitrectomy
- B-scan and EMI-scan Evaluation of Orbital Space-Occupying Lesions
- The Urokinase Central Retinal Vein Occlusion Trial
- Videotape Pupillometry
- Vitrectomy Perfusion Solutions

Macri, Frank J., M.D.
- Study of Pharmacodynamics of Various Agents Affecting the Intraocular Pressure

Laboratory of Vision Research

Section on Biochemistry

Kinoshita, Jin H., Ph.D.
- Cataracts
- Chemistry and Metabolism of the Lens

Chader, Gerald J., Ph.D.
- Cyclic Nucleotides and Vision
- Development and Function of the Retina, Pigment Epithelium and Cornea

Goldman, Arnold I., Ph.D.
- Ultrastructural and Biochemical Correlates in the Vertebrate Retina

Helmsen, Ralph J., Ph.D.
- Chemistry of the Cornea
- Induction of Buphthalmos in Chicks by Feeding a High Level of Glycine
- Mechanism of Herpes Simplex Virus Infection of Corneal Cells
- Vitamin A Metabolism of the Cornea

Hess, H. H., M.D.
- Biochemical Structure of Retina and Pigment Epithelium in Health and Disease

Lewis, Marc S., Ph.D.
- Chemistry of Rhodopsin
- Physical Chemistry of Model Gel Systems

Laboratory of Vision Research (cont.)

Section on Biochemistry (cont.)

O'Brien, Paul J., Ph.D.
Protein Synthesis in the Retina
Synthesis of Sugar-Containing Polymers in Retina

Shichi, Hitoshi, Ph.D.
The Membrane Biology of the Visual Process
The Molecular Pharmacology of the Eye

Whikehart, David R., Ph.D.
Intermediary Metabolism of the Cornea

Yoshikami, S., Ph.D.
The Visual Cell-Process of Photoexcitation

Section on Experimental Embryology

Coulombre, Alfred J., Ph.D.
Sensitive Period in the Development of the Scleral Ossicles of the Avian Eye

Newsome, David A., M.D.
Repair of DNA in Xeroderma Pigmentosum Conjunctiva

Zelenka, Peggy, Ph.D.
Plasma Membrane Composition and Biosynthesis in Chick Lens Fibers and Epithelia

Section on Experimental Pathology

Kuwabara, Toichiro, M.D.
Anatomical and Pathological Studies of Ocular Tissues
Effect of Laser on the Retina
Light Effect on the Retina

Robison, W. Gerald, Jr., Ph.D.
Ultrastructure and Function of the Pigment Cells of the Eye

Laboratory of Vision Research (cont.)

Section on Neurophysiology

De Monasterio, Francisco M., M.D., D.Sc.
Physiology of the Primate Visual System

Famiglietti, Edward V., Jr., M.D., Ph.D.
Anatomy of Mammalian Retina

Nelson, Ralph, Ph.D.
Electrophysiological Studies of Mammalian Retina

Office of Biometry and Epidemiology

Section on Clinical Trials and Natural History Studies

Ferris, Frederick L., III, M.D.
Development of a Standardized Visual Acuity Measuring Device
Development of a Visual Acuity Examination Technique to Evaluate Patient Bias

Section on Mathematical Statistics and Computer Applications

Milton, Roy C., Ph.D.
Statistical Support of a Cataract Etiology Study

Schwartz, J. Theodore, M.D.
Effect of Treatment on the Progression of Myopia

Yuen, Karen, Ph.D.
Comparison of Two Survival Curves
Non-Parametric Multi-Sample Location Tests Under Heteroscadasticity
Robustness of Some Sequential Statistical Procedures
Statistical Packaged Programs Design and Development
The Studentized Wilcoxon Statistic for the Behrens-Fisher Problem

Section on Epidemiology

Allen, David C., O.D., M.A.
Review of Eye Examination Data from National Health and Nutrition Survey

Office of Biometry and Epidemiology (cont.)

Section on Epidemiology (cont.)

Hiller, Rita, M.S.
- Prognosis for Life in Diabetics: Relation to Severity of Retinopathy
- Senile Cataract Extraction and Diabetes
- Sunlight and Cataract: An Epidemiologic Investigation

Yuen, Karen, Ph.D.
- On the Association of Female Hormones with Blindness from Diabetic Retinopathy